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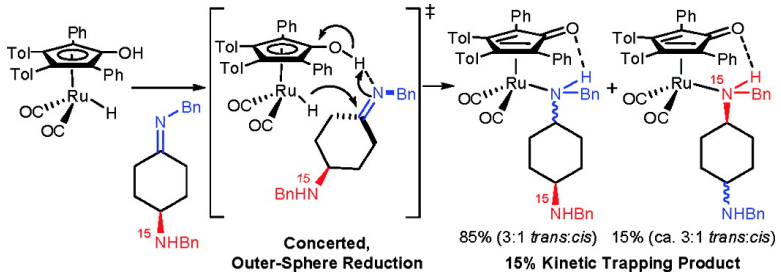
J. Am. Chem. Soc., **2007**, 129 (38), 11821-11827• DOI: 10.1021/ja073370x • Publication Date (Web): 31 August 2007



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Intramolecular Trapping of an Intermediate in the Reduction of Imines by a Hydroxycyclopentadienyl Ruthenium Hydride: Support for a Concerted Outer Sphere Mechanism

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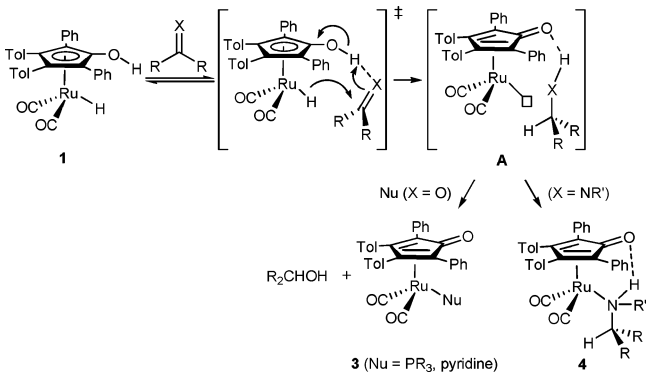
Abstract: Reduction of imines by [2,5-Ph_2-3,4-Tol_2(η^5-C_4COH)]Ru(CO)$_2$H (**1**) produces kinetically stable ruthenium amine complexes. Reduction of an imine possessing an intramolecular amine was studied to distinguish between inner sphere and outer sphere mechanisms. 1,4-Bn^{15}NH(*c*-C_6H_{10})═NBn (**12**) was reduced by **1** in toluene-d_8 to give 85% of [2,5-Ph_2-3,4-Tol_2(η^4-C_4CO)](CO)$_2$RuNHBn(*c*-C_6H_{10})^{15}NHBn (**16-RuN,^{15}N**), resulting from coordination of the newly formed amine to the ruthenium center, and 15% of trapping product [2,5-Ph_2-3,4-Tol_2(η^4-C_4CO)](CO)$_2$Ru^{15}NHBn(*c*-C_6H_{10})NHBn (**16-Ru^{15}N,N**), resulting from coordination of the intramolecular trapping amine. These results provide support for an outer sphere transfer of hydrogen to the imine to generate a coordinatively unsaturated intermediate, which can be trapped by the intramolecular amine. An opposing mechanism, requiring coordination of the imine nitrogen to ruthenium prior to hydrogen transfer, cannot readily explain the observation of the trapping product **16-Ru^{15}N,N**.

Introduction

The area of ligand−metal bifunctional catalysis has led to valuable methods for the hydrogenation of polar unsaturated organic substrates.[1−7] The first example of this type of catalyst, reported by Shvo and co-workers in 1986,[2−4] has been the subject of detailed mechanistic investigation[8] by both Bäckvall's group[9,10] and our group.[11−15] For the stoichiometric reduction of benzaldehyde by the active reducing agent, the hydroxycyclopentadienyl ruthenium hydride **1**, we found second-order kinetics and significant primary deuterium isotope effects for transfer of both OH and RuH.[11] We proposed an outer sphere mechanism involving concerted addition of the acidic hydroxy hydrogen and the hydridic ruthenium hydride to an unsaturated substrate (Scheme 1). DFT calculations supported this concerted outer sphere mechanism.[12] In contrast, Bäckvall has proposed an alternative inner sphere mechanism involving coordination of the heteroatom to ruthenium concurrent with η^5 to η^3 ring slippage of the hydroxycyclopentadienyl ligand, which precedes the concerted hydrogenation step (Scheme 2).[16,17]

Scheme 1. Concerted Outer Sphere Reduction Mechanism



Distinguishing between the inner (Scheme 2) and outer sphere (Scheme 1) reduction mechanisms is challenging due to the

(1) For reviews of ligand−metal bifunctional catalysis, see: (a) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73. (b) Noyori, R.; Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5356−5362. (c) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201−2237. (d) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393−406.
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(7) Fransson, A.-B. L.; Xu, Y.; Leijondahl, K.; Bäckvall, J.-E. *J. Org. Chem.* **2006**, *71*, 6309−6316.
(8) For mechanistic and computational work on other ligand−metal bifunctional hydrogenation catalyst systems, see: (a) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466−1478. (b) Abdur-Rashid, K.; Clapham, S. E.; Hadzovic, A.; Harvey, J. N.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 15104−15118. (c) Sandoval, C. A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490−13503. (d) Casey, C. P.; Johnson, J. B. *J. Org. Chem.* **2003**, *68*, 1998−2001. (e) Åberg, J. B.; Samec, J. S. M.; Bäckvall, J.-E. *Chem. Commun.* **2006**, 2771−2773.
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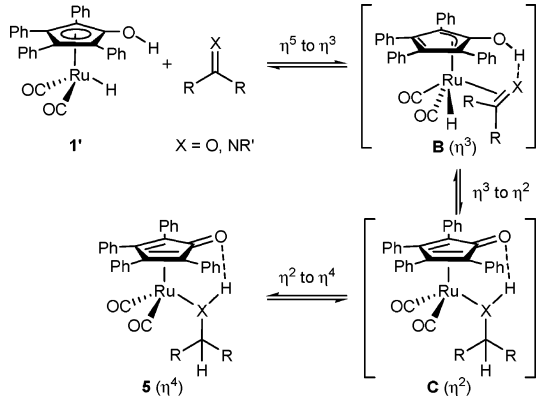
(16) Csjernyik, G.; Éll, A. H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1657−1662.

Scheme 2. Bäckvall's Concerted Inner Sphere Mechanism



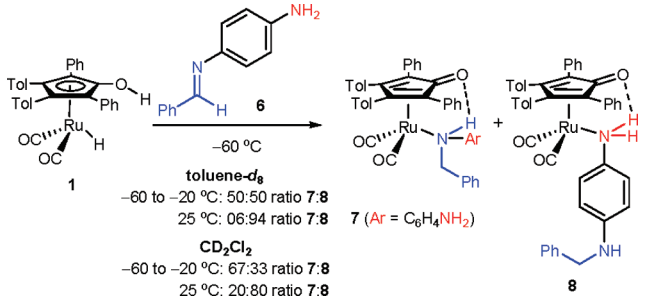
structural similarities between the first formed reactive intermediates **A** and **C**. In the outer sphere mechanism, the first formed intermediate upon reduction (**A**) is linked to the ruthenium complex by a hydrogen bond from the carbonyl oxygen of the cyclopentadienone ligand. In the inner sphere mechanism, the analogous intermediate links the newly reduced substrate to the complex by a Ru−X bond in addition to the hydrogen bond.

These mechanisms are potentially distinguishable based on trapping experiments. The outer sphere mechanism involves the coordinatively unsaturated intermediate **A**, which might be trapped prior to alcohol coordination, while the inner sphere mechanism leads directly to a coordinated alcohol. However, related ruthenium alcohol complexes have never been directly observed presumably because of rapid dissociation.[18,19] Consequently, recent mechanistic investigations in this area have focused on the reduction of imines by the Shvo complex because reduction produces kinetically stable amine complexes (**4**, Scheme 1).[10,12,14,15,18] The outer sphere mechanism predicts that intermediate **A** (Scheme 1) might be kinetically trapped by an added amine. In contrast, the inner sphere mechanism is more restrictive and requires the absence of kinetic trapping products.

Because the inner sphere mechanism results from pre-coordination of the imine to ruthenium, the inner sphere mechanism imposes two major restrictions not required by the outer sphere mechanism. First, in the inner sphere mechanism, the newly formed amine is "born" in the coordination sphere (**C**), which does not allow additional kinetic trapping agents to intercept the ruthenium if the complex is kinetically stable. The outer sphere mechanism permits (but does not require) inter- or intramolecular trapping of coordinatively unsaturated intermediate **A** by a trapping agent (Scheme 1). Second, stereospecific trans addition to an imine is required by the inner sphere mechanism due to pre-coordination and the required concerted transition state for reduction.[15] In contrast, the outer sphere mechanism allows both cis and trans reduction to occur.

Previous Trapping Experiments. In 2005, we reported inter- and intramolecular trapping experiments in the reduction of imines by ruthenium hydride complex **1**. We found that the

Scheme 3. Casey−Bikzhanova Intramolecular Trapping Experiment



reduction of an imine by **1** in the presence of an added amine led only to a ruthenium complex derived from the reduced imine. This result is that predicted by the inner sphere mechanism, but it might also be explained by formation of intermediate **A** within a solvent cage that collapsed to the ruthenium amine complex more rapidly than the amine could break its hydrogen bond to the cyclopentadienone carbonyl and escape from the solvent cage to be trapped by an external amine.

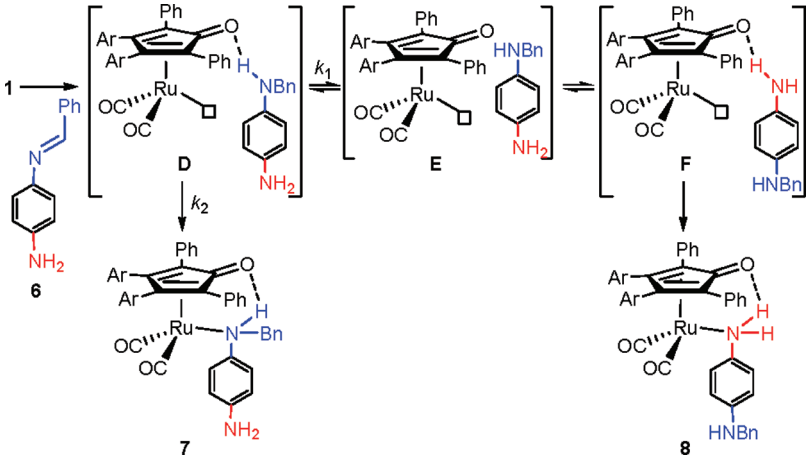
To distinguish between these two explanations, we turned to an intramolecular trapping experiment using the difunctional amino-substituted imine **6**. Reduction of imine **6** by **1** at reduced temperatures (≥−20 °C) in toluene-d_8 resulted in a 50:50 mixture of kinetically stable amine complexes **7** and **8** (Scheme 3).[12] Upon warming to 25 °C, the ratio of amine complexes shifted to a thermodynamic 94:6 ratio of **8**:**7**. Reduction of imine **6** by **1** in CD_2Cl_2 gave somewhat less of the intramolecular trapping product **8** (33%).[20]

These trapping experiments are consistent with an outer sphere reduction followed by competition between coordination of the newly formed amine and intramolecular trapping within the solvent cage.[21] For the trapping amine (shown in red, Scheme 4) to access the coordinatively unsaturated ruthenium center, the ligand-amine hydrogen bond of the newly formed amine (shown in blue) must be exchanged with the trapping amine via intermediate **E** (Scheme 4). The 50:50 ratio of **7**:**8** requires that the rate of hydrogen bond breaking (k_1) be faster than the rate of amine complexation (k_2).

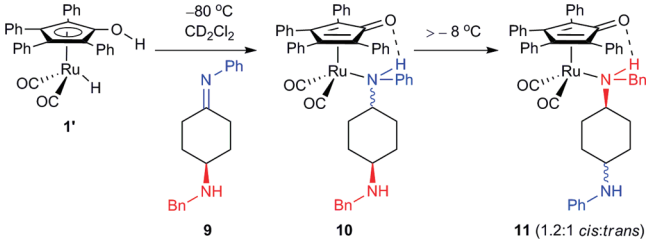
In 2006, Bäckvall reported an analogous intramolecular trapping experiment to probe the mechanism of imine reduction by **1′**.[10] Bäckvall considered the possibility that reduction of **6** occurred by an inner sphere mechanism but that the η^2 unsaturated intermediate (**C** in Scheme 2) might have undergone a "ruthenium migration via the aromatic system" to produce the intramolecular trapping product **8**.[22] He studied the reduction of the amine-substituted ketimine **9** in which the aromatic linker between the two nitrogen centers was replaced by a saturated

(17) Privalov, T.; Samec, J. S. M.; Bäckvall, J.-E. *Organometallics* **2007**, *26*, 2840−2848.
(18) Casey, C. P.; Bikzhanova, G. A.; Bäckvall, J.-E.; Johansson, L.; Park, J.; Kim, Y. H. *Organometallics* **2002**, *21*, 1955−1959.
(19) Casey, C. P.; Vos, T. E.; Bikzhanova, G. A. *Organometallics* **2003**, *22*, 901−903.
(20) Bikzhanova, G. A. Ph.D. Thesis, University of Wisconsin−Madison, 2005.
(21) Additional control experiments were consistent with cleavage of the amine hydrogen bond producing intermediate **E** and the diamine within the solvent cage. For example, the addition of an external amine (4-isopropylaniline) in the reduction of imine **6** only results in intramolecular and no intermolecular trapping products. Upon warming the 50:50 mixture of **7** and **8** to 24 °C, in the presence of the external amine, *p*-(*i*-Pr)$C_6H_4NH_2$, a 6:94 ratio of **7**:**8** was formed without the generation of the corresponding [*p*-(*i*-Pr)$C_6H_4NH_2$]−Ru complex. This result is consistent with a solvent cage effect.[12]
(22) DFT calculations by Privalov, Samec, and Bäckvall[17] have shown an energy minimum for a $Ru(CO)_2$ complex having an η^2-tetraphenylcyclopentadienone with one phenyl of the tetraphenyl cyclopentadienone bound η^2 to ruthenium. This suggests that ruthenium migration via the aromatic system might be possible.

Scheme 4. Outer Sphere Mechanism Model for Reduction of Imine **12**



Scheme 5. Bäckvall−Samec Intramolecular Trapping Experiment



linker (Scheme 5).[23] Reduction of **9** by ruthenium hydride **1′** in CD_2Cl_2 led only to the formation of ruthenium complex **10**, resulting from coordination to newly formed amine, and no detectable intramolecular trapping product **11** was observed. Complex **10** was kinetically stable up to −8 °C, at which point isomerization to the thermodynamically favored complex **11** was observed. Bäckvall concluded that this experiment provided support for the inner sphere mechanism (Scheme 2).

New Trapping Experiments. Bäckvall's preferred interpretation of these two intramolecular trapping experiments is that both proceed by an inner sphere mechanism but the Casey−Bikzhanova observation of a trapping product in the reduction of **6** resulted from migration of ruthenium across the π-system. An alternative interpretation is that both proceed by an outer sphere mechanism but that Bäckvall−Samec's failure to observe a trapping product in the reduction of **9** results from more rapid amine coordination than release of the amine hydrogen bond and formation of trapping product **11** (Scheme 6). Why might the relative rates of coordination to nitrogen as compared to breaking of the hydrogen bond be so much faster for intermediate **D′** from reduction of **9** (Scheme 6) than for intermediate **D** from reduction of **6** (Scheme 4)? We hypothesized that the hydrogen bond to the amine in **D (**derived from **6**) is weakened by electron donation from the *p*-amino substituent[24] and would be expected to break more readily and give rise to trapping products. To test this hypothesis, we designed imine **12**, which has an intramolecular trapping agent (Figure 1). In the outer sphere mechanism, reaction of **12** with **1** would generate an intermediate similar to **D**, having a weaker hydrogen bond than in the Bäckvall−Samec trap **9**, but without the intervening π-system of the Casey−Bikzhanova trap **6** that might cloud the results. In addition to the weakened hydrogen bond, the newly formed amine has increased nucleophilicity.[25] As a consequence of these two opposing effects (weakened hydrogen bond vs increased nucleophilicity), it is very difficult to predict how changes in the nature of the initially formed amine will affect the amount of trapping products observed. Here, we report the results of these new trapping experiments that provide support for an outer sphere reduction mechanism.

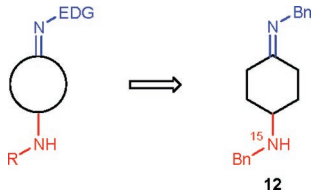


Figure 1. Imine substrate design.

Results

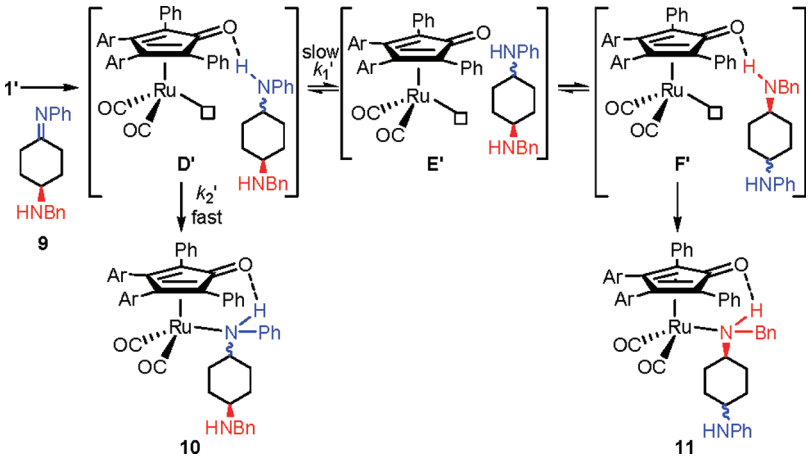
Design and Synthesis of Intramolecular Trapping Agent. The ^{15}N-labeled pseudo-symmetric imine **12** was designed to test this mechanistic hypothesis.[26] It offers three advantages: (1) The symmetrical diamine produced upon reduction has no thermodynamic preference for binding either amine to ruthenium. (2) ^{15}N NMR spectroscopy provides quantitative measurement of product ratios.[27] (3) The absence of an aryl linker simplifies interpretation of intramolecular trapping. Imine **12** was straightforwardly synthesized as shown in Scheme 7.[28]

Synthesis and Characterization of Ruthenium Diamine Complexes. Because the reduction of imine **12** was anticipated to produce cis and trans isomers of diamine ruthenium complexes, pure samples of unenriched ***trans*-16** and ***cis*-16** were independently synthesized (Scheme 8). Reductive amination of benzaldehyde with *trans*-1,4-cyclohexanediamine and $NaBH_4$ gave *N*,*N*′-dibenzyl-*trans*-1,4-cyclohexanediamine (***trans*-15**). Reaction of ***trans*-15** with {[2,5-Ph_2-3,4-Tol_2(η^4-C_4CO)]Ru-

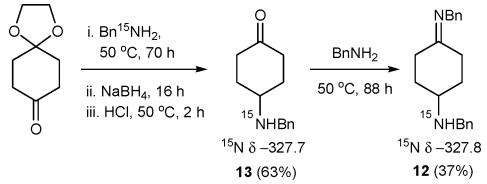
(23) See the Supporting Information for discussion of Bäckvall's observation[10] of an intermolecular trapping of an intermediate in the reduction of an imine by **1′** in the presence of an amine.

(24) We initially anticipated that the strength of the hydrogen bond of **D′** would be greater than that of **D** due to the increased electron donation from *p*-$NH_2C_6H_4$ versus Ph [*p*-$NH_2C_6H_4NH_3^+$ (pK_a = 6.08) is less acidic than anilinium $C_6H_5NH_3^+$ (pK_a = 4.58)]. During the review process, a referee pointed out that the cyclohexyl substituent of **D′** would weaken the hydrogen bond as compared to the benzyl substituent on **D** [$PhCH_2NH_3^+$ (pK_a = 9.30) is more acidic than *c*-$C_6H_{11}NH_3^+$ (pK_a = 10.64)]. These pK_a values nearly offset the anticipated difference between substrates **D** and **D′**. (a) Brown, H. C.; McDaniel, D. H.; Hafliger, O. Dissociation Constants. In *Determination of Organic Structures by Physical Methods*; Braude, E. A., Nachod, F. C., Eds.; Academic Press: New York, 1955; Vol. 1, p 590. (b) Hall, H. K., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5441−5444.

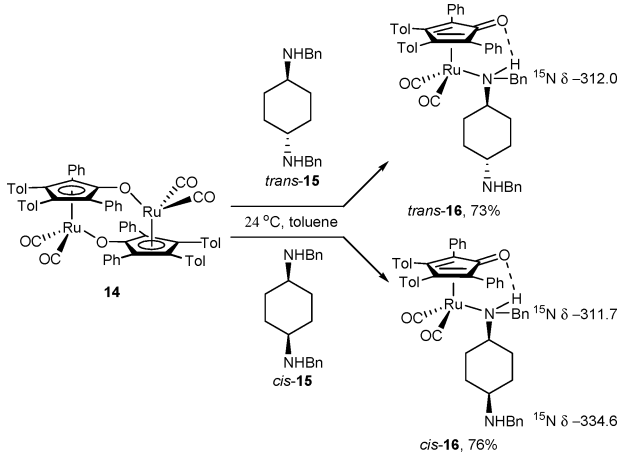
Scheme 6. Outer Sphere Mechanism Model for Reduction of Imine **9**



Scheme 7. Synthesis of Imine **12**



Scheme 8. Syntheses of ***cis*-16** and ***trans*-16**



$(CO)_2\}_2$ **14** gave ***trans*-16** (Scheme 8), which was characterized by X-ray crystallography (see the Supporting Information). Similarly, ***cis*-16** was prepared starting with *cis*-1,4-cyclohexanediamine.

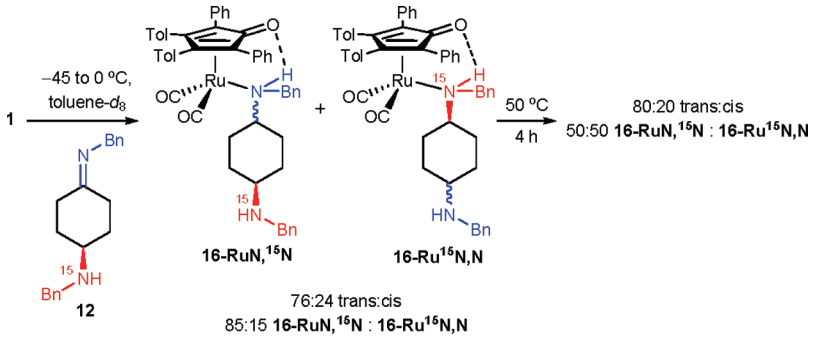
The ^{15}N-labeled **12** (δ −327.8) provided a good model for the ^{15}N NMR chemical shift of a free *N*-benzyl cyclohexyl amine.[29] The ruthenium complex of *N*-benzyl isopropylamine, [2,5-Ph$_2$-3,4-Tol$_2$(η^4-C$_4$CO)]Ru(CO)$_2$(*i*-PrNHBn) **17** (δ −308.0), provided a good model for the chemical shift of a *N*-benzyl cyclohexylamine ruthenium complex; its ^{15}N chemical shift was determined at natural abundance using a 2D ^{1}H−^{15}N HSQC NMR experiment. The 2D ^{1}H−^{15}N HSQC NMR spectrum of ***cis*-16** showed a strong cross-peak for the complexed amine at δ −311.7 and a less intense cross-peak for the free amine at δ −334.6.[30] The 2D ^{1}H−^{15}N HSQC NMR spectrum of ***trans*-16** showed only a strong cross-peak for the complexed amine at δ −312.0; no cross-peak for the free amine was observed in this natural abundance experiment.[31]

Low-temperature Trapping Experiments were conducted with ^{15}N-labeled imine **12** in toluene-d_8 at −45 °C. Reaction of **12** (0.11 M) with ruthenium hydride **1** occurred below −45 °C. ^{15}N NMR spectra at −45 °C showed complete disappearance of **12** and broad resonances in the δ −300 to −330 range. ^{15}N NMR spectra obtained at 0 °C gave sharp resonances whose ratios did not change over time at 0 °C. Four peaks were observed in the ^{15}N NMR spectrum at 0 °C: δ −334.66 (21%, ***cis*-16-RuN,^{15}N**), −324.63 (64%, ***trans*-16-RuN,^{15}N**), −311.29 (12%, ***trans*-16-Ru^{15}N,N**), and −310.95 (~3%, ***cis*-16-Ru^{15}N,N**). Overall, this corresponds to a 76:24 ratio of trans:cis diamine complexes. About 15% of **16** has the original ^{15}N-labeled amine coordinated to ruthenium, while 85% of **16** has the nitrogen derived from the newly formed amine coordinated to ruthenium.[27]

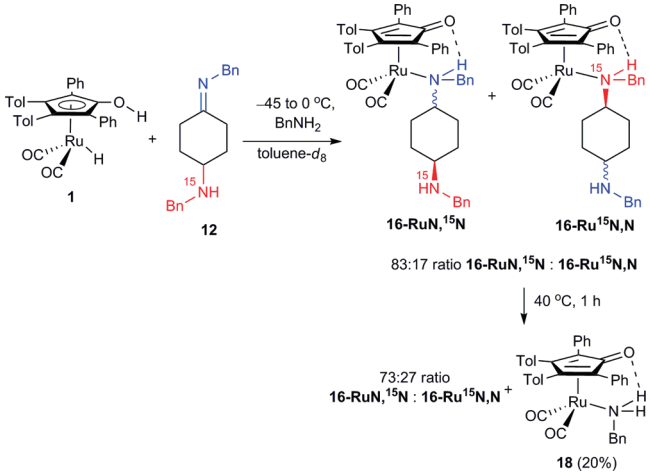
The initial ratio of isomeric complexes of **16** was unchanged up to 24 °C, demonstrating that the ratios observed at 0 °C are kinetically determined. Upon heating at 50 °C, the ratio of isomers of **16** changed somewhat after 2 h and reached a steady state after 4 h (Scheme 9).[32] The intensities of the four ^{15}N NMR resonances indicated a 40:40:10:10 ratio of ***trans*-16-RuN,^{15}N**:***trans*-16-Ru^{15}N,N**:***cis*-16-RuN,^{15}N**:***cis*-16-Ru^{15}N,N**. Thus, the^{15}N-label was evenly distributed between the free amine and the coordinated amine in both the cis and the trans isomers. In terms of the outer sphere mechanism, this requires breaking both the N−Ru bond and the hydrogen bond of the amine to the dienone carbonyl, followed by coordination of one of the equivalent

(25) The nucleophilicity parameters of amines (*N*) are known to deviate largely from pK_a values, suggesting that the rates of hydrogen-bond breakage (k_1, Scheme 4) and amine complexation (k_2) are not just dependent on the pK_a value. For example, PhNH$_3^+$ (pK_a = 4.58, *N* = 12.99 in water) is 0.71 pK_a units more acidic than *p*-CH$_3$OC$_6$H$_4$NH$_3^+$ (pK_a = 5.29, *N* = 16.53 in water), but is 3.54 *N* units less nucleophilic. Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679−3688.
(26) Bäckvall also used ^{15}N NMR analysis in his trapping experiments.[10]
(27) An inverse gated pulse sequence and a relaxation delay of 35 s were used to allow quantitative comparisons of ^{15}N NMR integrals.
(28) A similar strategy was employed by Bäckvall for the synthesis of imine **9**.[10]
(29) ^{15}N NMR chemical shifts are reported on the δ scale with respect to nitrobenzene as the standard.
(30) See the Supporting Information.
(31) Coupling of the unbound nitrogen to the NH hydrogen averages to zero due to rapid exchange processes. This was confirmed by obtaining a non-decoupled ^{15}N NMR spectrum of the products of reduction of **12** that showed no coupling between ^{15}N and ^{1}H for ***trans*-16-RuN,^{15}N**.
(32) Upon heating the products of the reduction of **12** by **1** to 50 °C, three decomposition products were observed in addition to isomers of **16**. One of the decomposition products observed upon heating was identified as bisruthenium diamine complex {[2,5-Ph$_2$-3,4-Tol$_2$(η^5-C$_4$CO)]Ru(CO)$_2$}$_2$-{μ-[*trans*-1,4-(BnNH)-*c*-C$_6$H$_{10}$(N HBn)]} (**^{15}N-23**). See the Supporting Information.

Scheme 9. Trapping Experiment: Reduction of Imine **12** by **1**



Scheme 10. Reduction of Imine **12** by **1** in the Presence of Benzylamine



nitrogens of the diamine. The rate of isomerization of dialkyl amine complex **16** is slower than that seen earlier for the aryl, alkyl amine complexes resulting from reduction of imines **6** and **9**, which occurred at lower temperatures. This is attributed to greater basicity of the dialkyl amine. The change in the ^{15}N label distribution upon heating further confirms the kinetic nature of the initial ratio of isomers.

It was also noted that the ratio of trans:cis isomers increased from 3:1 to 4:1 upon heating. This was independently investigated by heating the unlabeled ***cis*-16** in toluene-d_8 at 50 °C for 2 h. Formation of a ~4:1 equilibrium mixture of ***trans*-16**:***cis*-16** was observed by ^{1}H NMR spectroscopy. This cis−trans equilibration is best explained by reversible dehydrogenation of ***cis*-16** back to **12** and **1**. We have previously observed reversible hydrogenation of imines by **1** as a required process in imine isomerization.[14,15,33]

The reduction of imine **12** by **1** in the presence of benzylamine (1:1 ratio) in toluene-d_8 was studied to determine if intermolecular kinetic trapping occurred at low temperatures (Scheme 10). ^{1}H NMR spectroscopy showed less than 5% of the benzylamine complex **18** (low intensity of resonance at δ 3.1) was formed. Upon heating at 40 °C for 1 h, approximately 20% of **18** was formed concurrent with an increase from 17% to 27% of products with the ^{15}N label bound to ruthenium. Thus, the rate of intramolecular scrambling of ^{15}N-label is similar to the rate of intermolecular amine exchange. Previously, we had seen more rapid intramolecular amine exchange between **7** and **8** than intermolecular amine exchange with *p*-isopropylaniline.[12]

(33) For a more detailed discussion of benzylamine as an intermolecular trap in the reduction of imine **12** by **1**, see the Supporting Information.

Reduction of imine **12** by complex **1** was also examined in CD_2Cl_2 at −20 °C. Four peaks were observed in the ^{15}N NMR spectrum at −20 °C: δ −335.2 (9%, ***cis*-16-RuN,^{15}N**), −322.7 (82%, ***trans*-16-RuN,^{15}N**), −311.9 (7%, ***trans*-16-Ru^{15}N,N**), and −311.3 (~2%, ***cis*-16-Ru^{15}N,N**). This corresponds to an 89:11 ratio of trans:cis isomers, which is higher than that seen in toluene-d_8. In CD_2Cl_2, more of the nitrogen coordinated to ruthenium was derived from the newly formed amine (91%). The decreased amount of **16** with the ^{15}N-labeled amine coordinated to ruthenium (9%) in CD_2Cl_2 is similar to the decreased quantity of trapping product **8** observed from imine **6** (Scheme 3, 50% in toluene-d_8 and 33% in CD_2Cl_2).

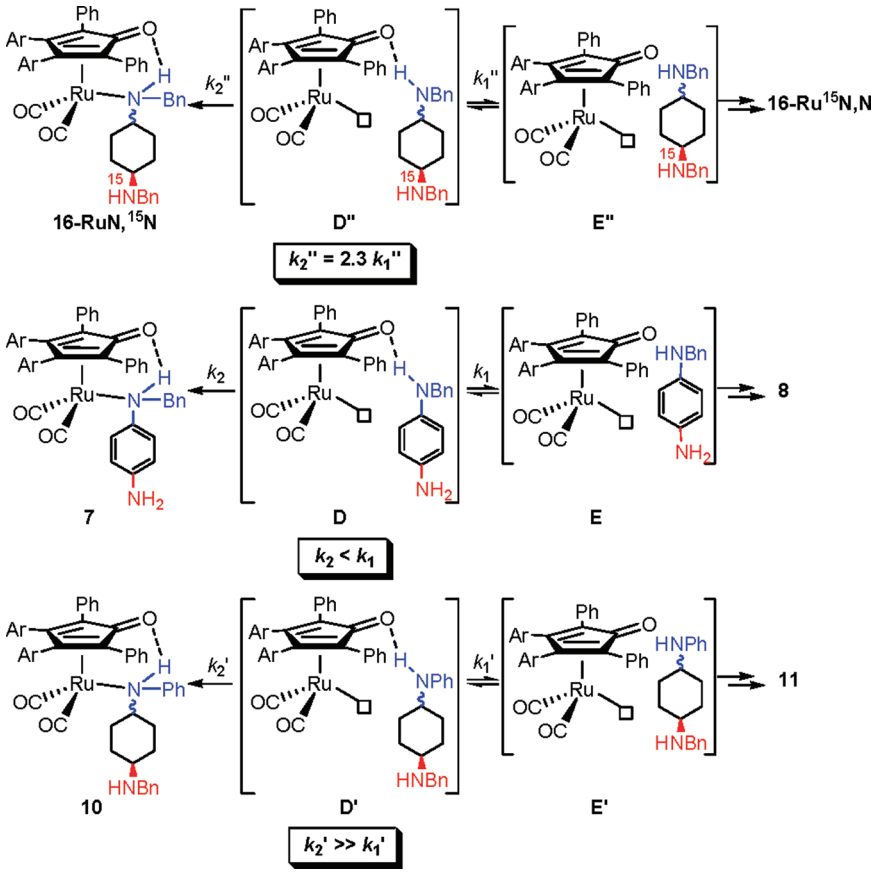
Discussion

The possibility that the formation of trapping product **16-Ru^{15}N,N** is an artifact of the experimental conditions and results from a small amount of rearrangement of the **16-RuN,^{15}N** was given serious consideration. If the reaction mixture was inadvertently warmed during insertion into the pre-cooled NMR probe, a small amount of rearrangement of **16-RuN,^{15}N** to **16-Ru^{15}N,N** could have occurred upon warming. This possibility can be excluded because the amine complex rearranges extremely slowly at room temperature and requires heating at 50 °C for 4 h to reach equilibrium (Scheme 9).

The kinetic formation of ***trans*-16-Ru^{15}N,N** and ***cis*-16-Ru^{15}N,N** requires the intervention of a coordinatively unsaturated intermediate and is consistent with an outer sphere reduction mechanism (Scheme 9). These trapping products cannot result from "ruthenium migration via the aromatic system"[10] as Bäckvall suggested as a route to intramolecular trapping product **8** in an inner sphere mechanism. The observation of these trapping products provides strong support for an outer sphere mechanism (Scheme 1) and is inconsistent with an inner sphere mechanism involving hydroxycyclopentadienyl ring slippage (Scheme 2).

Because the coordinatively unsaturated intermediate is not intermolecularly trappable, coordination of the newly formed amine to ruthenium must be much faster than diffusion from the solvent cage.[12] The presence of a hydrogen bond from the newly formed amine to the dieone carbonyl could help to explain slow diffusion of the amine from the solvent cage.[12] In the case of intramolecular trapping agents, we need to explain why more than one-half of the product is derived from coordination of the newly formed amine. Again, hydrogen bonding of the newly formed amine to the dienone carbonyl can explain selective coordination of the new amine.[12] For intramolecular trapping, the hydrogen bond must be broken to give a solvent cage containing the unsaturated intermediate and a free diamine.

Scheme 11. Partitioning of Unsaturated Intermediates between Hydrogen Bond Breaking (k_2) and Amine Coordination (k_2)

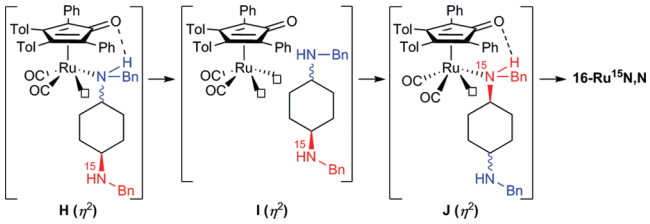


Hydrogen bonding to either amine can then occur within the solvent cage followed by coordination to ruthenium. Escape of the diamine from the solvent cage therefore requires both breaking of hydrogen-bonding interactions and diffusion apart.

For the three different intramolecular trapping experiments, the product ratios depend on the relative rates of coordination of the newly formed amine (k_2) and breaking of the hydrogen bond to the newly formed amine (k_1). Both of these rates should be faster for a more electron-rich amine, which would be both more nucleophilic and also a weaker hydrogen-bond donor. While both k_1 and k_2 are expected to increase with increased electron-rich amines, Mayr has found that the correlation between the nucleophilicity parameter N and the pK_{aH} value is poor.[25] Therefore, it is impossible to predict the dependence of this rate ratio (and the amount of trapping product) on the structure of the amine.

The extent of intramolecular trapping product formation provides a measure of the relative rates of amine coordination (k_2) and of hydrogen bond breaking (k_1) (Scheme 11). For the reduction of **12** by **1** in toluene-d_8, the 85:15 ratio **16-RuN,^{15}N**:**16-Ru^{15}N,N** is explained by 70% immediate coordination of the newly formed amine and 30% breaking of hydrogen bond (to form **E**″) that can result in coordination of either diamine nitrogen ($k_{2''}/k_{1''} = 2.3$) (Scheme 11). For the reduction of Bäckvall's imine **9** by **1**′ in CD_2Cl_2, the observation of only the product (**10**) from coordination of the newly formed amine suggests that coordination of the amine is much faster than breaking of the relatively strong hydrogen bond to the aryl amine ($k_{2'}/k_{1'} \gg 1$). The strength of the hydrogen bond allows

Scheme 12. Pathway to Trapping Products in Inner Sphere Mechanism

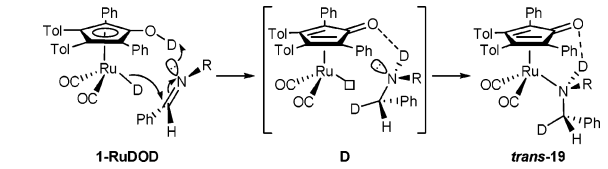


coordination before hydrogen bond breaking occurs. For the reduction of Casey and Bikzhanova's imine **6** in toluene-d_8, the observation of a 50:50 ratio of **7**:**8** indicates that amine coordination is a bit slower than hydrogen bond breaking ($k_2/k_1 < 1$). It should also be noted that less trapping product was observed from **6** in CD_2Cl_2 than in toluene-d_8, suggesting that k_2/k_1 is larger in CD_2Cl_2.[34]

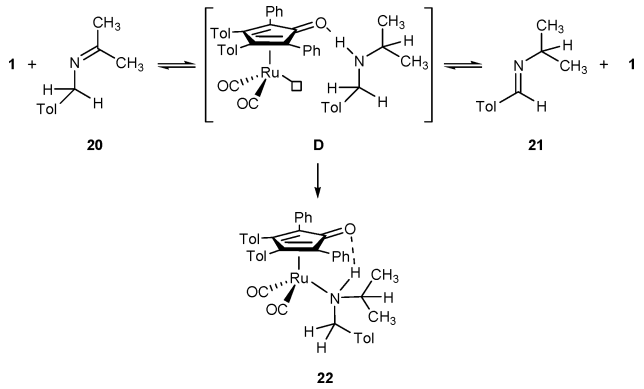
Additional Constraints on the Inner Sphere Mechanism To Account for Observed Trapping Products. While the outer sphere mechanism provides a consistent explanation for all of the data that have been reported, an inner sphere mechanism requires a competing process for the generation of 9−15% trapping products **16-Ru^{15}N,N** from the reduction of imine **12**. Bäckvall has suggested that the initially formed η^2-16 e- ruthenium amine complex (**H**, Scheme 12) could dissociate the amine, followed by re-coordination of the alternative amine

(34) The formation of complexes **16-RuN,^{15}N** and **16-Ru^{15}N,N** from intermediate **E**″ could also proceed directly from **E**″ to the respective amine complex without a hydrogen-bonded intermediate [**D**″ or **F**″ (analogous to **F**′ in Scheme 6)]. This variation in the mechanism does not change the conclusions described in the text.

Scheme 13. Stereochemistry of Imine Reduction



Scheme 14. Reversible Imine Reduction



nitrogen (Scheme 12). We believe that this process would not be kinetically competent because it requires extremely rapid cleavage of the Ru−N bond of **H** at 0 °C and generation of a very high-energy 14 e- ruthenium complex **I**. It is highly unlikely that dissociation of the Ru−N bond of **H** would be much faster than the dissociation of amine from **16-RuN,^{15}N**, which requires heating at 50 °C.

Very High Reactivity of the Coordinatively Unsaturated Intermediate. The coordinatively unsaturated intermediate **D**, with an amine hydrogen bonded to the dienone carbonyl, displays unusually high reactivity. The collapse of this intermediate by coordination of nitrogen to ruthenium occurs faster (for **D′** and **D″**) than breaking the weak hydrogen bond between the amine and a dienone carbonyl and much faster than hydrogen bond breaking followed by diffusion apart. Earlier we demonstrated that hydrogenation of an imine occurred with some selectivity for trans addition of dihydrogen (Scheme 13). This stereospecificity requires that the coordination of the newly formed amine to ruthenium occurs more rapidly than lone pair inversion at the nitrogen center. In the case of the reduction of *N*-alkyl imines by **1**, we found isomerization and deuterium scrambling evidence for reversible imine hydrogenation (Scheme 14). Reversible hydrogenation requires that unsaturated intermediate **D** transfer hydride back from carbon to ruthenium faster than amine coordination to nitrogen.

Conclusion

Intramolecular trapping of an intermediate in the reduction of imine **12** by ruthenium hydride **1** provides strong support for an outer sphere mechanism for imine reduction. We infer that the reduction of other polar unsaturated substrates such as ketones and aldehydes proceeds by similar mechanisms.

Experimental Section

1,4-BnN=(*c*-C$_6$H$_{10}$)^{15}NHBn (12). A solution of ketone **13** (0.750 g, 3.69 mmol) and benzylamine (0.480 mL, 4.43 mmol) in 10 mL of benzene containing 4 Å mol sieves (ca. 1 g) was heated at 50 °C for 88 h. The reaction mixture was filtered through Celite and concentrated in vacuo. Imine **12** was obtained as a yellow oil (0.40 g, 37%) by bulb-to-bulb distillation (135−145 °C/0.08 mmHg). ^{1}H NMR (C_7D_8, 500 MHz) δ 7.47 (d, J = 8.0, 2H), 7.30 (d, J = 8.0, 2H), 7.26 (m, 4H), 7.13 (m, 2H), 4.47 (d, J = 15.7, 1H), 4.44 (d, J = 15.4, 1H), 3.57 (d, J = 13.6, 1H), 3.56 (d, J = 13.2, 1H), 2.63 (dt, J = 11.5, 5.2, 1H), 2.48 (ddd, J = 12.2, 8.5, 3.5, 1H), 2.36 (m, 1H), 2.15 (m, 1H), 1.73 (m, 1H), 1.3 (m, 1H), 1.57 (m, 1H), 1.32 (m, 1H), 1.12 (m, 1H), 0.72 (br s, 1H). ^{13}C NMR (C_6D_6, 125 MHz) δ 172.0, 142.1, 128.93, 128.92, 128.69, 128.67, 128.5, 127.5, 127.0, 54.9 (d, J = 4.4), 54.8, 51.6 (d, J = 4.4), 37.3 (d, J = 1.4), 33.7 (d, J = 2.1), 32.9 (d, J = 2.9), 26.0 (d, J = 1.4). ^{15}N NMR (C_7D_8, 50.7 MHz) δ −327.8. IR (thin film) 3060, 3026, 2925, 2856, 1658, 1494, 1452 cm^{-1}. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{25}N^{15}N$ $(M + H)^+$ 294.1988, found 294.1979.

Low-Temperature Reduction of Imine 12 by 1 in Toluene-d_8. A solution of [2,5-Ph$_2$-3,4-Tol$_2$(η^4-C$_4$COH)]}Ru(CO)$_2$H (**1**) in toluene-d_8 was prepared as previously described[11] by heating a solution of {-[2,5-Ph$_2$-3,4-Tol$_2$(η^5-C$_4$CO)]$_2$H}Ru$_2$(CO)$_4$(μ-H) (0.023 g, 0.020 mmol) in THF-d_8 (0.4 mL) in a medium-walled resealable NMR tube under 1 atm H_2 at 90 °C for 14 h. Solvent was evaporated under vacuum, and the residue was dissolved in toluene-d_8 (0.15 mL). The solution of **1** in toluene-d_8 was frozen in liquid nitrogen, and a solution of imine **12** (0.20 mL, 0.040 mmol, 0.2 M **12** in toluene-d_8) was added under nitrogen gas. The tube was sealed, warmed to −78 °C, and inserted into a pre-cooled (−45 °C) NMR spectrometer. ^{15}N NMR spectra at −45 °C showed three broad resonances: δ −334.6 (***cis*-16-RuN,^{15}N**), −324.2 (***trans*-16-RuN,^{15}N**), −310.2 (***trans*-16-Ru^{15}N,N**). The NMR probe was warmed to 0 °C, and a second ^{15}N NMR spectrum showed four resonances: δ −334.7 (21%, ***cis*-16-RuN,^{15}N**), −324.6 (64%, ***trans*-16-RuN,^{15}N**), −311.3 (12%, ***trans*-16-Ru^{15}N,N**), −311.0 (∼3%, ***cis*-16-Ru^{15}N,N**). The sealed NMR tube was then heated at 50 °C for 4 h in an oil bath. An ^{15}N NMR spectrum at 0 °C showed the four expected resonances, δ −334.7 (10%, ***cis*-16-RuN,^{15}N**), −324.6 (40%, ***trans*-16-RuN,^{15}N**), −311.3 (40%, ***trans*-16-Ru^{15}N,N**), −311.0 (10%, ***cis*-16-Ru^{15}N,N**), and three new resonances, δ −310.1 due to {[2,5-Ph$_2$-3,4-Tol$_2$(η^5-C$_4$CO)]Ru(CO)$_2$}$_2${μ-[*trans*-1,4-(Bn^{15}NH)-*c*-C$_6$H$_{10}$-(NHBn)]} **^{15}N-23** (about the same integration as the δ −324.6 and −311.3 resonances), and two unassigned resonances at δ −324.4 (about one-half the integration of the δ −324.6 and −311.3 resonances) and −312.7 (about one-third the integration of the δ −324.6 and −311.3 resonances).

Acknowledgment. Financial support was provided by the Department of Energy, Office of Basic Energy Sciences, the National Science Foundation (CHE-0209476), and the National Institutes of Health in the form of a NRSA fellowship to T.B.C. (GM077962-01). Grants from the NSF (CHE-9629688) and NIH (I S10 RR04981-01) for the purchase of NMR spectrometers are acknowledged. We thank Dr. Galina A. Bikzhanova for insightful discussions, Ms. Lara Spencer for assistance with X-ray crystallography, and Drs. Charles Fry and Monica Ivancic for assistance with NMR spectrometry.

Supporting Information Available: General experimental information, syntheses of **13**, ***trans*-15**, and ***cis*-15**, and ruthenium complexes ***trans*-16**, ***cis*-16**, and **17**, selected ^{15}N NMR spectra, and X-ray crystal structures of ***trans*-16** and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA073370X