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Mechanistic Study of Hydrogen Transfer to Imines from a Hydroxycyclopentadienyl Ruthenium Hydride. Experimental Support for a Mechanism Involving Coordination of Imine to Ruthenium Prior to Hydrogen Transfer

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Abstract: Reaction of [2,3,4,5-Ph_4(η^5-C_4COH)Ru(CO)$_2$H] (**2**) with different imines afforded ruthenium amine complexes at low temperatures. At higher temperatures in the presence of **2**, the complexes decomposed to give [Ru_2(CO)$_4$(μ-H)(C_4Ph_4COHOCC_4Ph_4)] (**1**) and free amine. Electron-rich imines gave ruthenium amine complexes with **2** at a lower temperature than did electron-deficient imines. The negligible deuterium isotope effect (k_{RuHOH}/k_{RuDOD} = 1.05) observed in the reaction of **2** with *N*-phenyl[1-(4-methoxyphenyl)ethylidene]-amine (**12)** shows that neither hydride (RuH) nor proton (OH) is transferred to the imine in the rate-determining step. In the dehydrogenation of *N*-phenyl-1-phenylethylamine (**4**) to the corresponding imine **8** by [2,3,4,5-Ph_4(η^4-C_4CO)Ru(CO)$_2$] (**A**), the kinetic isotope effects observed support a stepwise hydrogen transfer where the isotope effect for C−H cleavage (k_{CHNH}/k_{CDNH} = 3.24) is equal to the combined (C−H, N−H) isotope effect (k_{CHNH}/k_{CDND} = 3.26). Hydrogenation of *N*-methyl(1-phenylethylidene)amine (**14)** by **2** in the presence of the external amine trap *N*-methyl-1-(4-methoxyphenyl)ethylamine (**16)** afforded 90−100% of complex [2,3,4,5-Ph_4(η^4-C_4CO)]Ru(CO)$_2$NH(CH_3)(CHPhCH_3) (**15**), which is the complex between ruthenium and the amine newly generated from the imine. At −80 °C the reaction of hydride **2** with 4-BnNH−C_6H_9═NPh (**18**), with an internal amine trap, only afforded [2,3,4,5-Ph_4(η^4-C_4CO)](CO)$_2$RuNH-(Ph)(C_6H_{10}-4-NHBn) (**19**), where the ruthenium binds to the amine originating from the imine, showing that neither complex **A** nor the diamine is formed. Above −8 °C complex **19** rearranged to the thermodynamically more stable [Ph_4(η^4-C_4CO)](CO)$_2$RuNH(Bn)(C_6H_{10}-4-NHPh) (**20**). These results are consistent with an inner sphere mechanism in which the substrate coordinates to ruthenium prior to hydrogen transfer and are difficult to explain with the outer sphere pathway previously proposed.

Introduction

Transition metal-catalyzed hydrogen transfer has attracted considerable attention during the past 10−15 years.[1,2] A variety of new catalysts have been reported that are highly efficient for transferring hydrogen from a hydrogen donor (e.g., an alcohol) to a hydrogen acceptor (e.g., a ketone). Catalytic hydrogen transfer reactions have been successfully applied to selective organic transformations including enantioselective reactions.[3] In 1985 Shvo reported on the dimeric catalyst **1** as an efficient hydrogenation catalyst for various substrates including ketones and aldehydes. Catalyst **1** breaks up into the monomers **2** and **A** (Scheme 1),[4] and the former monomer (**2**) is able to hydrogenate a hydrogen acceptor whereas the latter monomer (**A**) can dehydrogenate a hydrogen donor. These processes interconvert **2** and **A**. Complex **1** has been shown to be active in the disproportionation of aldehydes to esters and in the hydrogenation of carbonyl compounds to alcohols.[5] Our group discovered the advantages of **1** in Oppenauer-type oxidations[6] of alcohols where the catalyst was found to be stable in the presence of molecular oxygen.[6a] It was later shown that catalyst **1** is an efficient catalyst for racemization of alcohols, and this was used in combination with lipases for dynamic kinetic

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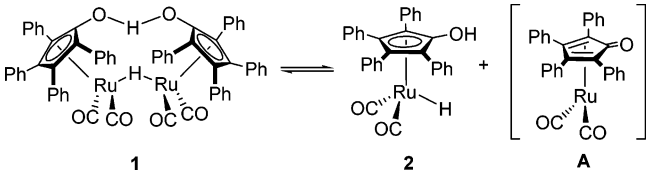
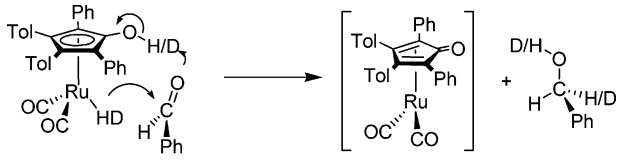
Scheme 1. Dimeric Precatalyst **1** in Equilibrium with Active Monomers **2** and **A**



Scheme 2. Hydrogenation of Benzaldehydes by **2′** and Proposed Concerted Outer-Sphere Mechanism



KIE

$k_{RuHOH/RuDOD} = 3.6$

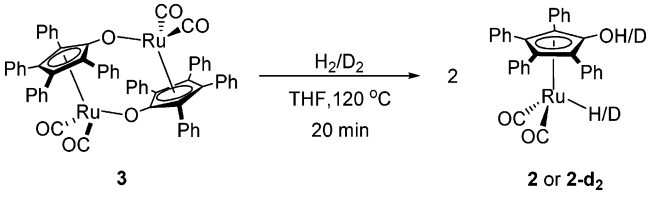
$k_{RuHOH/RuHOD} = 2.2$

$k_{RuHOH/RuDOH} = 1.5$

resolution of secondary alcohols where catalyst **1** showed a remarkable stability toward long reaction times.[7] We have reported that **1** can be successfully used as a catalyst for the reduction of imines,[8] oxidation of amines,[9] and racemization of amines,[10] via hydrogen transfer. Recently, a slightly modified catalyst **1** (Ph replaced by *p*-MeO−C_6H_4) was successfully combined with a lipase to give a highly efficient dynamic kinetic resolution of primary amines.[11]

We and others have studied the mechanism of this catalyst in the hydrogen transfer reactions involving various substrates.[3,5,9b,12−16] Casey and co-workers[13] determined the kinetic deuterium isotope effect in the reaction of **2′** with benzaldehyde and found that selective deuteration of either the hydroxy or hydride position of **2′** gave individual isotope effects (1.5, 2.2) in agreement with the combined isotope effect (3.6) observed for **2′** deuterated in both positions. Casey and co-workers[13] proposed a mechanism where the hydride and the acidic proton of **2** are transferred in a concerted manner to the carbonyl outside the coordination sphere of the metal (Scheme 2). We subsequently found that also for the reversed reaction, the dehydrogenation of 2-(4-fluorophenylethyl)ethanol, there were significant individual deuterium isotope effects (1.9, 2.6) correlating to the combined isotope effect (4.6), indicating a simultaneous hydrogen transfer from alcohol to **A**.[14] In the latter case we also considered an alternative inner-sphere pathway via coordination of alcohol to ruthenium in addition to the outer sphere pathway.

Scheme 3. Generation of Active Species **2**



Here we report on a detailed mechanistic study involving the reactions of imines with the active species **2** of Shvo's catalyst **1**. At low temperatures ruthenium−amine complexes are formed when **2** reduces imines. A correlation was found between the electronic properties of the imine and the temperature at which the complexation between the imine and **2** begins. Kinetic isotope effect studies for (*i*) the stoichiometric reaction of **2** with a ketimine[17] and (*ii*) the catalytic dehydrogenation of an amine by **A**[9b] clearly show that the rate-limiting step in the mechanism operating for imines and amines is different from that proposed for ketones (aldehydes) and alcohols.[13,18] Reduction of an imine with **2** in the presence of either an external amine trap in the presence of H_2 or an internal amine trap gave only amine complexes from the newly generated amine. This is consistent with an inner sphere mechanism in which the substrate coordinates to ruthenium prior to hydrogen transfer and is difficult to explain with the outer-sphere mechanism previously proposed.[13,15]

Results and Discussion

A. Starting Material Synthesis. Complex **2** was prepared from [2,3,4,5-Ph_4(η^4-C_4CO)$Ru_2(CO)_2]_2$ (**3**) in THF-d_8 in a microwave oven reactor at 120 °C under H_2 for 20 min to afford the complex in total conversion (Scheme 3).[19] The imines were prepared from the appropriate amine and ketone via a base-catalyzed condensation.[8]

B. Formation of Ruthenium Amine Complexes. In catalytic hydrogen transfer reactions of imines and amines using catalyst **1**, a correlation between the electronic property of the substrate and the rate of the reaction was observed.[8−10] Thus, in the transfer hydrogenation of imines[8] and transfer dehydrogenation of amines,[9] as well as in the racemization of chiral amines,[10] electron-rich *N*-alkyl imines reacted faster than the corresponding electron-deficient *N*-aryl imines.[20] The concerted outer-sphere mechanism originally proposed[13] for the reduction of benzaldehyde by hydride **2′** does not adequately explain the inverse isotope effect observed for electron-rich *N*-alkyl imines. In the refined mechanism recently published by Casey,[15,16] these effects are accounted for by assuming that the concerted addition is a reversible step, followed by a rate-determining coordination of the generated amine to ruthenium. It was pointed out that the acidity of the CpOH and basicity of the imine should increase the rate due to a late transition state in the imine reduction.[16] The in general higher reactivity of imines over ketones toward **2** (**2′**) is in contrast to what Noyori has found for the well studied ligand−metal bifunctional catalyst RuH-[TosCH(C_6H_5)CH(C_6H_5)NH_2](η^6-arene),[21] where ketones react faster than imines.[22]

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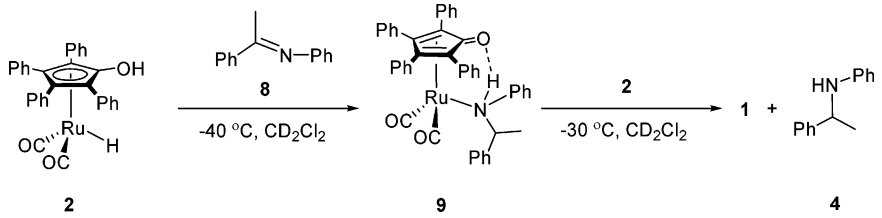
(19) Casey has prepared this complex in a very similar way; see ref 13.

(20) Except for very electron-rich N-alkyl imines, which formed thermostable ruthenium amine complexes that inhibited further catalysis.

Scheme 4. Stable Ruthenium Amine Complexes Are Formed at Low Temperatures

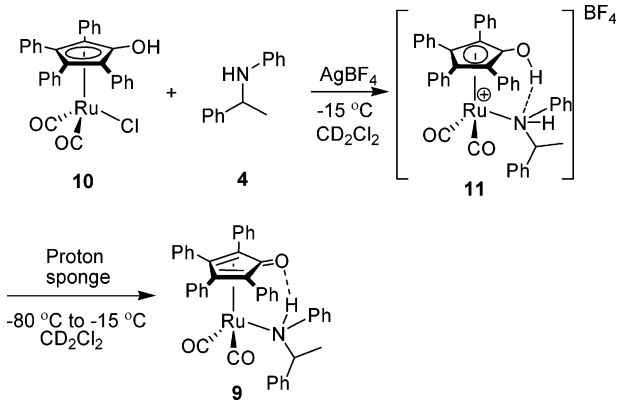


In the catalytic transfer hydrogenation of *N*-phenyl imines in benzene−2-propanol with **1** as catalyst, no ruthenium amine complexes with the products were observed.[8a,23] Attempts to synthesize a ruthenium amine complex from a reaction of [2,3,4,5-$Ph_4(\eta^4$-$C_4CO)]Ru(CO)_3$ (**5**) with *N*-phenyl-1-phenylethylamine (**4**), using the procedure described by Shvo for the preparation of the ruthenium benzylamine complex, failed.[24] When MeN═CHPh (**6**) was employed as substrate in the catalytic transfer hydrogenation with **1** no reaction occurred at 70 °C.[25] Analysis by ^{1}H NMR spectroscopy revealed that the reaction had been inhibited by formation of a ruthenium amine complex [2,3,4,5-$Ph_4(\eta^4$-$C_4CO)Ru(CO)_2NH(Me)(CH_2Ph)]$ (**7**). At reflux in toluene a reaction occurred but only slowly (20% conversion to amine after 2 h using 1 mol % of **1**) due to strong complexation between the product and ruthenium.

When *N*-phenyl(1-phenylethylidene)amine (**8**) was used as the imine substrate in the reaction with ruthenium hydride **2** (1.1 equiv) the buildup of [2,3,4,5-$Ph_4(\eta^4$-$C_4CO)Ru(CO)_2NH$-$(Ph)(CH_3CHPh)]$ (**9**) started at −40 °C as shown by ^{1}H NMR spectroscopy (Scheme 4). Complex **9** appeared as two diastereomers. The major isomer has characteristic resonances at δ 0.86 (d, J = 6.4 Hz, 3H), 3.46 (d, J = 11.0 Hz, 1H), 4.47 (dq, J = 6.4, 11 Hz, 1H). When the doublet at 0.86 ppm was homodecoupled the doublet of a quartet at 4.46 became a doublet with J = 11 Hz, and when the doublet at 3.6 was homodecoupled the doublet of a quartet at 4.46 became a quartet with J = 6.4 Hz.[26] The minor isomer has characteristic resonances at δ 1.49 (d, J = 8.3 Hz, 3H), 4.32 (brd, J = 7.1 Hz, 1H), 4.49 (m, 1H). When the temperature was raised to −30 °C in the presence of **2**, the free amine (**4**) appeared with characteristic ^{1}H NMR resonances at δ 1.48 (d, J = 6.4 Hz, Me), 4.32 (d, J = 5.5 Hz, NH), 4.46 (dq, J = 6.4, 5.5 Hz, CH), and **1**, with the characteristic hydride resonance at −18.75 (Scheme 4). Note that, in the absence of **2**, amine complex **9** is stable at temperatures above −30 °C.

Complex **9** was also prepared in situ by a similar technique as that used for preparation of cationic ruthenium alcohol complexes.[27] The complex was prepared by mixing [2,3,4,5-$Ph_4(\eta^5$-$C_4COH)Ru(CO)_2Cl]$ (**10**), $AgBF_4$, and amine **4** in CD_2Cl_2 in an NMR tube at −15 °C overnight. The resulting protonated ruthenium amine complex **11**, formed in situ, was

Scheme 5. Alternative Route to Ru−Amine Complexes



cooled to −80 °C and a sterically hindered proton sponge (1,8-bis(dimethylamino)naphthalene) was added. The mixture was shaken, and the NMR tube was inserted into a precooled spectrometer at −15 °C, and deprotonation of **11** afforded complex **9** that was observed by ^{1}H NMR (Scheme 5). Interestingly, this shows that complex **9** is stable at −15 °C in the absence of hydride **2**.

Reaction of **2** with *N*-(phenyl)-1-(*p*-methoxyphenylethylidene)amine **12** led to a buildup of the concentration of [2,3,4,5-$Ph_4(\eta^4$-$C_4CO)]Ru(CO)_2NH(4$-MeO−Ph$)(CHCH_3Ph)$ (**13**) already at −58 °C (Table 1, entry 2). Complex **13** was obtained as a mixture of diastereomers with characteristic ^{1}H NMR resonances at δ 0.81 (d, J = 6.4 Hz, Me), 3.34 (d, J = 11 Hz, NH), 3.57 (s, MeO), 4.50 (dq, CH), 5.56 (Ar), and 5.97 (Ar) (major isomer) and at δ 3.65 (s, MeO), 1.47 (d, J = 6.4 Hz, Me) (minor isomer). These diastereomeric complexes were stable in the presence of **2** until −25 °C when the free amine with characteristic ^{1}H NMR resonances at δ 1.46 (d, J = 6.0 Hz, Me), 3.76 (s, MeO), and 4.44 (q, J = 6.0 Hz, CH) appeared (Table 1, entry 2).

To investigate the electronic effects, the electron-withdrawing *N*-phenyl group was replaced by an *N*-methyl group. Reaction of *N*-methyl imine **14** with **2** gave the most stable amine complex (**15**) of the three complexes compared (Table 1, entry 3). Complex **15** was formed below −78 °C, and the diastereoisomers have characteristic ^{1}H NMR resonances at δ 3.91, 3.31, 1.93, 1.25 (major isomer) and at δ 3.45, 3.27, 1.02 (minor isomer). At this temperature it was difficult to distinguish the signals because of broadening. When the temperature was raised a better resolved spectrum was obtained (see Experimental Section). Both diastereomers of complex **15** were isolated by column chromatography and characterized. Complex **15** was stable in the presence of complex **2** until 47 °C. At this temperature complex **15** decomposed into an unidentified species with ^{1}H NMR resonances at δ 3.33 (s), 2.86 (m) 0.95 (s), which are different from those of the corresponding amine.

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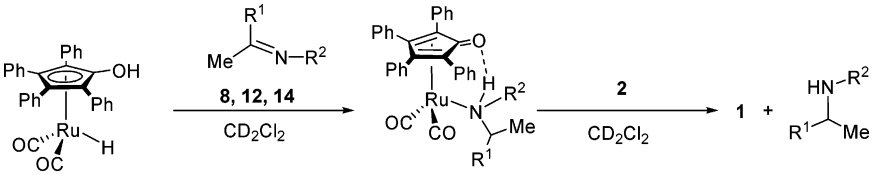
(22) It was recently found that reaction of RuH[TosCH(C_6H_5)CH(C_6H_5)NH_2]-(η^6-arene) with imines requires activation by an added acid: Åberg, J. B.; Samec, J. S. M.; Bäckvall, J. E. *Chem. Commun.* **2006**, 2771.
(23) However with a methyl group on the nitrogen, an amine complex was observed.
(24) Abed, M.; Goldberg, I.; Stein, Z.; Shvo, Y. *Organometallics* **1988**, *7*, 2054.
(25) Samec, J. S. M. Dissertation, Stockholm University, 2005.
(26) When the reaction was run in THF-d_8 the complex appeared as diastereomeres with doublets at δ 0.88 and 0.92; both had a coupling constant of J = 6.5 Hz.
(27) Casey C. P.; Vos T. E.; Bikzhanova G. A. *Organometallics* **2003**, *22*, 901

Table 1. Correlation of the Electronic Property of the Imine and the Stability of the Complex[a]



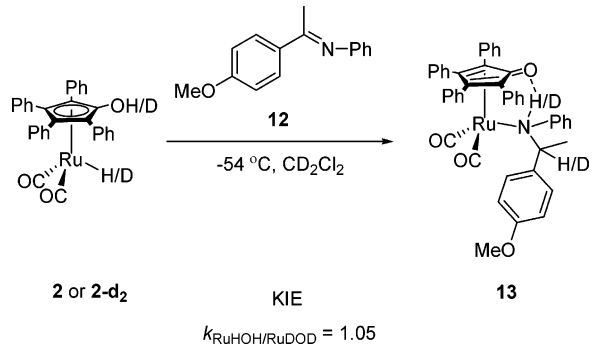
2

9 R^1 = Ph R^2 = Ph
13 R^1 = *p*-MeO-Ph R^2 = Ph
15 R^1= Ph R^2=Me

entry	imine	substituents	complex	temperature of complexation (°C)	temperature of decomplexation (°C)
1	**8**	R^1 = Ph R^2 = Ph	**9**	−40	−30
2	**12**	R^1 = *p*-MeO−Ph R^2 = Ph	**13**	−58	−25
3	**14**	R^1 = Ph R^2 = Me	**15**	below −78	47

[a] Reaction conditions: **2** (0.06 mmol, 0.12 M, 0.5 mL) was cooled to −196 °C in an NMR tube. The imine (0.03 mmol, 0.3 M, 0.1 mL) was carefully added making sure the solution froze before mixing with **2**. The NMR tube was then transferred to a dry ice acetone bath where the solutions were carefully mixed. The NMR tube was then cooled to −196 °C and inserted to a precooled spectrometer. The temperature in the spectrometer was determined using MeOH.

Scheme 6. Kinetic Isotope Effect of Hydrogenation of Imine **12** by **2**



2 or **2-d$_2$** KIE **13**

$k_{RuHOH/RuDOD}$ = 1.05

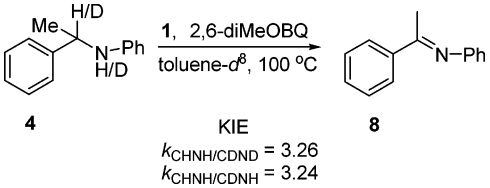
C. Kinetic Isotope Effect. To elucidate whether the hydrogen transfer is rate-determining or not, we carried out kinetic isotope effect studies for the hydrogen transfer from **2** to ketimine **12**. Stoichiometric hydrogenation of **12** in CD_2Cl_2 was carried out at −54 °C using an excess of **2** and **2-d$_2$** (Ru−D, O−D) (Scheme 6).[17] The product of the reaction at this temperature is the ruthenium amine complex **13**. The reaction is readily followed by ^{1}H NMR spectroscopy since the methoxy signals of imine **12** and amine complex **13** appear at different shifts. Imine **12** has the methoxy signal at δ 3.85, whereas the two diastereomers of complex **13** have their methoxy signals at δ 3.62 and 3.55 where the former is the major isomer. The reactions were run under pseudo-first-order kinetics with an excess of **2** until over two half-lives were over (24 min) integrating the methoxy peaks of imine **12** versus the two peaks of complex **13**.

The rate of the formation of **13** for RuHOH was $k_{obs} = (1.24 \pm 0.08) \times 10^{-3}$ s^{-1}, and that for RuDOD was $k_{obs} = (1.18 \pm 0.09) \times 10^{-3}$ s^{-1}.[28] The kinetic isotope effect calculated from these results is therefore $k_{RuHOH}/k_{RuDOD} = 1.05 \pm 0.14$. This is in sharp contrast to the corresponding kinetic isotope effect observed for benzaldehyde which was 3.6 (Scheme 2). The latter isotope effect shows that the transfer of hydrogen from ruthenium and oxygen to the aldehyde occurs within the rate-determining step.[11] *The low isotope effect of 1.05 for the transfer of hydrogen from **2** to imine **12** shows that a mechanism different from that of the aldehyde operates, since the hydrogen transfer is not the rate-determining step.* The low isotope effect may have several explanations of which a rate-determining coordination of the imine substrate to ruthenium is one.[29] This will be discussed below.

We have also found that the deuterium isotope effects for the reverse transfer dehydrogenation of *N*-phenyl-1-phenylethylamine (**4**) to the corresponding imine **8** are best explained by a stepwise mechanism.[9b] As the active species **A** in dehydrogenation cannot be isolated, and also because the reaction is reversible with the equilibrium strongly shifted toward the amine, stoichiometric experiments are difficult to perform. One way to circumvent these problems is to study the kinetics under catalytic conditions. By using 2,6-dimethoxybenzoquinone as a hydrogen acceptor, the reaction can be studied under conditions where species **2** is quickly recycled back to active species **A**. The kinetic deuterium isotope effect of the hydrogen transfer from **4** to active species **A** can therefore be obtained from the overall isotope effect of the catalytic reaction.[30] Interestingly, there is a large isotope effect for the cleavage of the C−H bond of the amine ($k_{CHNH}/k_{CDNH} = 3.24$), and importantly, this individual isotope effect for the C−H cleavage is equal within experimental error to the combined isotope effect for C−H and N−H cleavage ($k_{CHNH}/k_{CDND} = 3.26$). *This clearly shows that the rate determining step is cleavage of the C−H bond and that the transfer of the hydrogen from the amine to complex **A** cannot be a concerted process* (Scheme 7). The kinetic isotope effect for the transfer of the hydrogen from the nitrogen to the oxygen is small, and it is dependent on whether the α-carbon of the amine is deuterated or not ($k_{CHNH}/k_{CHND} = 1.39$) and ($k_{CDNH}/k_{CDND} = 1.01$), which shows that the difference in rate

(28) Seven and six different experiments, respectively, were run for RuHOH and RuDOD individually.
(29) Casey's group has also performed a kinetic isotope study on different aldimines and found that very electron-deficient imines behave as aldehydes and electron-rich imines give inverse isotope effects. See ref 15.
(30) It has been established that dehydrogenation of amine **4** is much slower than hydrogen transfer from hydride **2** to the quinone when an excess of quinone is used. Furthermore, the former dehydrogenation step is an irreversible step under these conditions.[9]

Scheme 7. Kinetic Isotope Effect for the Dehydrogenation of **4** by **1**



between C−H cleavage and N−H cleavage is not very large.[31] The results obtained for amine **4** are in sharp contrast to the corresponding dehydrogenation of alcohols where the individual isotope effects (1.9 and 2.6) were in agreement with the combined isotope effect (4.6).[14]

D. Imine Reduction in the Presence of a Potential External Amine Trap. To elucidate if the imine is coordinated to the catalyst during the hydrogen transfer, exchange studies were performed. If the outer-sphere mechanism was operating for imines, the hydrogen-bonded amine of complex **X** (**A** + amine) would have to coordinate to ruthenium to give complex **B** more rapidly than it dissociates to give **A** to avoid the competing reaction of **2** with **A** to give dimer **1** (Scheme 8, Path A). However, if the imine coordinates to ruthenium prior to the hydrogen transfer forming intermediate **C** (Scheme 8), the nitrogen would stay coordinated and give complex **B** without the presence of free complex **A** during the reaction (Scheme 8, Path B).

One way to distinguish between the two different pathways would be to have another amine, similar to the product amine, present in equimolar amounts (Scheme 9). In Path A of Scheme 8, if **X** dissociated to give **A** and an amine, the newly produced amine and the added amine would compete to associate with complex **A**. If **X** more rapidly dissociates to a new amine and **A** than it collapses to amine complex **15**, then early in the reaction **A** will be trapped by the more abundant added amine to give trapping product **17**. Later in the reaction as the concentration of the new amine builds up, amine complexes **15** and **17** will form; with equimolar amounts of **2**, ketimine **14**, and amine trap **16**, more than 50% of the trapping product would be expected. In path B there would be no incorporation of added amine in the amine complex and only **15** should be formed.

Reaction of hydride complex **2** with the unsubstituted imine **14** in the presence of equimolar amounts of *p*-methoxy substituted amine **16** gave the amine complexes **15** and **17** in a ratio of 90:10 (Scheme 9, Table 2 entry 1). This ratio did not change with time at −20° over 2 h.[32]

The predominant formation of **15** (Scheme 9), which is the complex between the ruthenium and the newly generated amine, provides strong support for Path B in Scheme 8, in which the imine is coordinated during the hydrogen transfer. The formation of complex **17** could in principle be explained by an outer-sphere mechanism[13] and is seemingly inconsistent with an inner-sphere mechanism. An outer-sphere mechanism in which **X** more rapidly dissociates to a new amine and **A** than it collapses to amine complex **15** can be excluded since it should have led to >50% **15**. The observed 10% formation of external trapping product **17** might be explained in the outer-sphere mechanism by a cage effect where the hydrogen-bonded amine of complex **X** coordinates to ruthenium to give complex **15** more rapidly than it dissociates to give **A**.[15,16] The ratio of **15:17** (90:10) did not change when the amount of trapping amine **16** was varied from 0.5 to 2 equiv (Table 2).

One possibility for the formation of **17** could be that **2** is contaminated with trace amounts of **3**, which could react with the free amine. With the detection limit we have this could only account for <5% of **17**.[33] Another explanation is that hydrogen is lost from **2** during the reaction giving the active intermediate **A** and its dimeric form **3**.[34] The free amine **16** in solution would then react with either **A** or **3** to give **17**. Loss of hydrogen at −20 °C seems less likely since loss of hydrogen usually requires much higher temperatures.[34] Yet another possibility could be that some exchange occurs via dissociation of the amine in the η^2-cyclopentadienone complex **D** (Scheme 14) before it rearranges to the stable η^4 complex **B**. When the reaction of **14** and **16** with **2** was carried out in the presence of H_2 no formation of **17** was observed (Table 2, entry 4). The disappearance of product **17** in the presence of H_2 suggests that the small amount of exchange product (10% relative yield) originates from an unsaturated species **A** formed in the reaction.

E. Imine Reduction in the Presence of a Potential Internal Amine Trap. The results from the above exchange studies with an external amine trap, where a predominant formation of a ruthenium amine complex with the amine produced from the imine was observed, could in principle be explained by a cage effect in an outer-sphere mechanism. This would require that the diffusion of the formed amine from the solvent cage (see Scheme 8, Path A) would be slower than the coordination of the amine to **A**. This was recently proposed[15] and supported by the observation that the internal trap (*p*-NH_2−C_6H_4N=CHPh) gave an exchange.[16] Thus, hydrogenation of *p*-NH_2−C_6H_4N=CHPh by **2′** gave a 1:1 mixture of the two possible amine complexes [2,5-Ph_2-3,4-Tol_2(η^4-C_4CO)]$(CO)_2$RuNH(CH_2Ph)(C_6H_4-*p*-NH_2) and [2,5-Ph_2-3,4-Tol_2(η^4-C_4CO)]$(CO)_2$Ru$NH_2C_6H_4$-*p*-$NHCH_2$Ph. This outcome is expected if the free diamine and **A** are formed in an outer-sphere process. However, the nitrogens of the diamine formed in the latter study were connected by a benzene ring, and one cannot exclude the possibility that the internal exchange could occur via the π-system of the aromatic ring where ruthenium can slip over from one nitrogen to the other. In the present study, we have therefore chosen a substrate, which gives a diamine where the nitrogens are connected by a saturated cyclohexane ring instead of a benzene ring.

At low temperatures the reaction of hydride complex **2** with 4-($PhCH_2NH$)−C_6H_9=NPh (**18**) afforded only amine complex [2,3,4,5-Ph_4(η^4-C_4CO)]Ru$(CO)_2$NH(Ph)(C_6H_{10}-4-($NHCH_2$Ph)) (**19**), where the newly formed amino group is coordinated to ruthenium (Scheme 10). Hydride **2** and imine

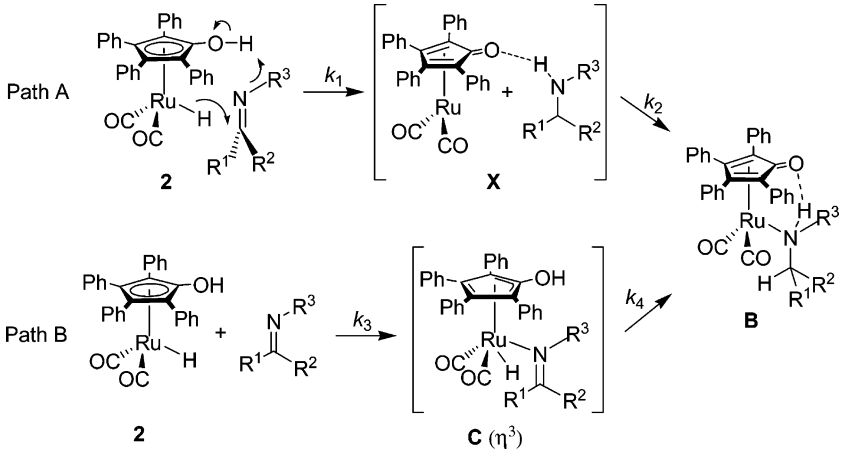
(31) When the α-carbon is deuterated in amine **4**, the transfer of N−H and N−D will both be fast in relation to C−D cleavage and cannot be distinguished. On the other hand when the α-carbon is nondeuterated, the α-carbon−hydrogen bond cleavage is >3 times faster compared to the deuterated case and the difference in rate between transfer of the N−H and N−D can be partly seen.

(32) It was not possible to detect any free amine PhCH(Me)NHMe from reduction of imine **14** in the NMR spectrum.

(33) It is not straightforward to detect contamination of **3** in **2** since there are no distinguishable peaks for **3** in the ^{1}H NMR of **2**. We were finally able to use ^{13}C NMR for detection of **3** in **2** (see Supporting Information). However, the detection limit of the dimer is about 2%. With 2% of **3** up to ca. 4% of trapping complex could be formed.

(34) Casey and co-workers have recently studied how substrates such as alcohols, phosphines, and even water promote the H_2 elimination from **2**. See: Casey, C. P.; Johnson, J. B.; Singer, S. W.; Cui, Q. *J. Am. Chem. Soc.* **2005**, *127*, 3100.

Scheme 8. Exchange Study



Scheme 9. Exchange Study with External Amine Trap **16**

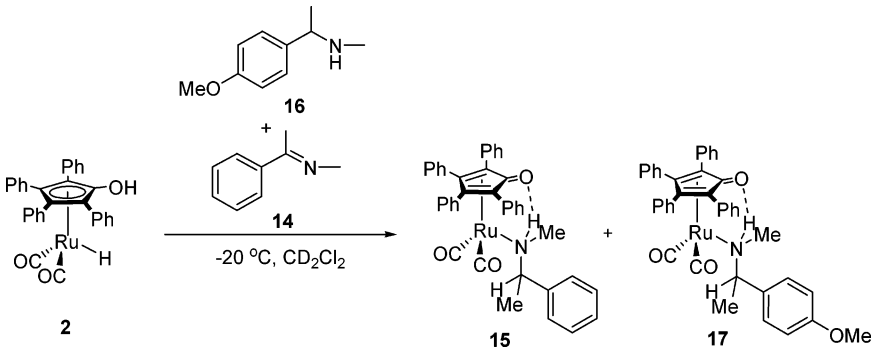


Table 2. Reaction of **2** and Imine **14** in the Presence of External Amine Trap **16**[a]

entry	atmosphere	equiv of amine **16**	ratio of **15:17**
1	argon	1	90:10
2	argon	0.5	90:10
3	argon	2	90:10
4	H_2	1	100:0

[a] The reactions were run by adding 0.1 mL of imine **14** (1 M) and 0.1 mL of amine **16** (0.5, 1, 2 M) to a 0.4 mL 0.25 M solution of **2** at −196 °C, mixed at −78 °C and analyzed by ^{1}H NMR at −20 °C for 20 min.

18 were mixed at <−100 °C in an NMR tube in CD_2Cl_2 and followed by ^{1}H NMR. Complex **19** started to build up already at −80 °C with broad characteristic benzyl signals at δ 3.5 ppm readily distinguishable from the benzyl resonance of the imine **18** at δ 3.75 ppm. The temperature was then carefully raised (10−15 °C per h). Complex **19** was stable until −8 °C. At this temperature the benzyl signals of complex **19** slowly decreased and new signals (overlapping AB parts of two ABX spectra) appeared at δ 3.54−3.86 ppm. The new signals correspond to [2,3,4,5-Ph_4(η^4-C_4CO)]Ru(CO)$_2$NH(CH_2Ph)-(C_6H_{10}-4-(NHPh)) (**20**), the complex where ruthenium binds to the amine of the trap. The spectrum was assigned by comparison with a ^{1}H NMR spectrum of a reference sample of *cis*- and *trans*-**20** (see below).

^{15}N NMR experiments were also carried out where the imine nitrogen part of **18** was marked with ^{15}N. The imine gives a characteristic resonance at δ −60 ppm in the ^{15}N NMR. The ^{15}N-marked imine was mixed with **2** in CD_2Cl_2 in an NMR tube at <−100 °C and inserted into a precooled spectrometer. At −80 °C one signal appeared at δ −296 ppm, which was assigned to complex **19**.[35,36] The resonance at δ −296 ppm persisted until −8 °C, and at this temperature two new resonances appeared at δ −294 and −304 ppm, which corresponds to the two diastereomers of complex **20** (reference samples of *cis*- and *trans*-**20**, ^{15}N labeled at the anilinic nitrogen, confirmed this assignment). The complex appears as two diastereomers (cis:trans 1.2:1) due to the cis/trans mixture of the cyclohexane diamine ligand. The free amine appears at δ −299 ppm. The failure to see trapping products either from an external trap in the presence of H_2 or from an intramolecular trap provides strong support for an inner-sphere mechanism. An outer-sphere mechanism can only account for the failure to see intramolecular trapping products with the severe restriction that the hydrogen-bonded amine of complex **X** coordinate to ruthenium to give **19** much more rapidly than it breaks the hydrogen bond to give **A** and the diamine within a solvent cage (Scheme 8, Path B).

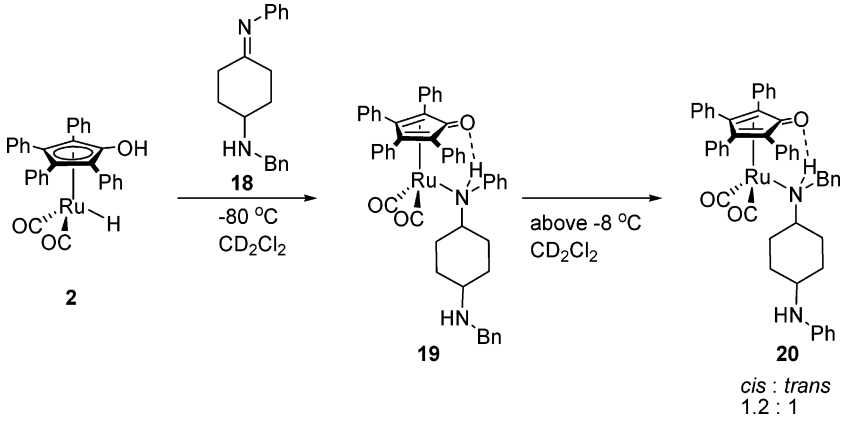
Amine complex **20** was independently synthesized from complex **3** and the diamine **21** (Scheme 11). A diastereomeric mixture of diamine **21** (cis/trans = of 2:3) afforded complex **20** as a cis/trans diastereomeric mixture in a ratio of 2:3. Both diastereomers were isolated as pure isomers by column chromatography and fully characterized.

F. X-ray Structures of the Diastereomers of 20. The pure diastereomers *cis*- and *trans*-**20** were crystallized from methylene chloride and hexane to give crystals that were suitable

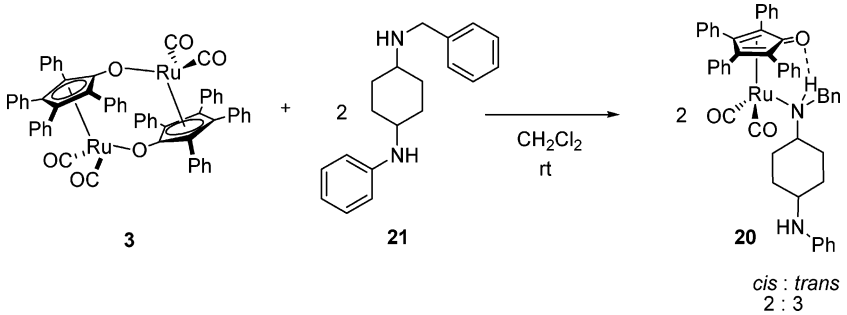
(35) The corresponding ruthenium complex with ^{15}*N*-cyclohexylaniline, which was prepared from reaction of C_6H_{10}=^{15}NPh (C_6H_{10} = cyclohexylidene) with **2** gave a signal at δ −297 ppm.

(36) To confirm that this signal was not a protonated form of **18** a control experiment was run where the imine was mixed with TFA; no signal at δ −296 ppm was observed.

Scheme 10. Exchange Study Using an Internal Amine Trap (Bn = CH_2Ph)



Scheme 11. Alternative Pathway for the Formation of Complex **20** (Bn = CH_2Ph)



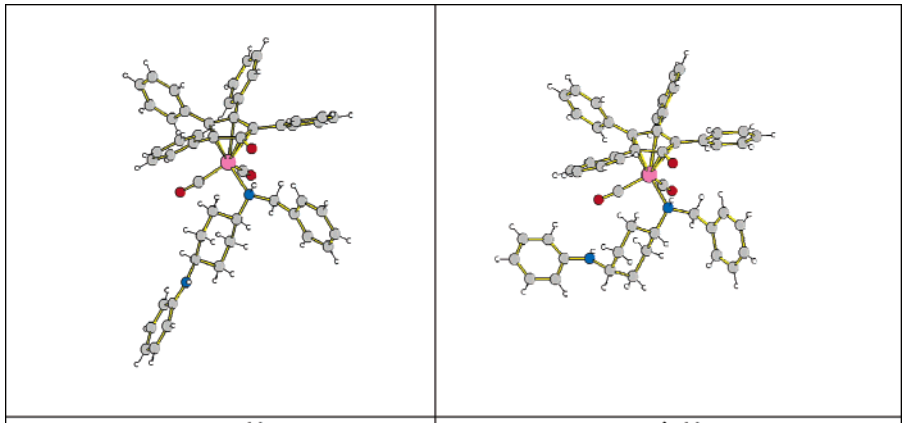
for X-ray crystallography. The X-ray crystal structures of *cis*- and *trans*-**20** are given in Figure 1. Shvo has reported an analogous X-ray structure of a complex generated from diethylamine,[24] and Casey has determined X-ray structures of the corresponding complexes of primary amines.[13,16,37] The X-ray structures of the trans and cis isomers of complex **20** are similar to those previously reported in the literature for related ruthenium amine complexes.[16,24,37] The Ru atom is formally pentacoordinated with a bidentate (η^4-Ph_4C_4CO) ligand, two CO groups, and either the cis or the trans diastereoisomer of the corresponding diamine **21**, respectively. The Ru−C1 distance is 2.448(3) Å for the trans isomer and 2.419(5) Å for the cis isomer. The C1 atom is displaced from the plane defined by atoms C2, C3, C4, and C5 in the trans complex by 0.142(4) Å and in the cis complex 0.141(8) Å. The envelope angle of the Cp-ring defined as the angle between the plane defined by C2, C3, C4, and C5 and the plane defined by C2, C1, and C5 is 9.1(3)° for the trans isomer and 9.2(2)° for the cis isomer. The deviation of the oxygen atom from the latter plane (defined by C2, C1, and C5) is 0.19(1) Å in the direction to the hydrogen of the amine coordinated to ruthenium for the trans compound and 0.16(1) Å in the direction to the amine hydrogen for the cis compound. The CO distance of the Cp-ring is 1.258 (4) Å in the trans compound and 1.257(7) Å in the cis isomer. The oxygen of the carbonyl in the Cp-ring is slightly pointing downward toward the amine ligand by 0.150(6) Å for *trans*-**20** and 0.181(12) Å for *cis*-**20** in relation to the least-squares plane defined by the carbons C2, C3, C4, and C5 in the Cp-ring due to the shared hydrogen bond. The average distance Ru−C2 and Ru−C5 is 2.26(1) Å for the trans compound and 2.27(1) Å for the cis complex, and the average distance Ru−C3 and Ru−C4 is 2.20(1) Å for both the trans and cis isomers. The two torsion angles from the cyclohexane group via the aniline are 161.5° and 76.0° in the trans complex of **20** and, as expected, inversed namely 76.9° and 160.4° in the cis complex of **20**.

Mechanistic Discussion

Casey originally proposed a mechanism for ketones (aldehydes) and also imines that proceeds via a concerted hydrogen transfer outside the coordination sphere of ruthenium (Scheme 12).[13] In the case of imines, the amine produced would coordinate to **A′** after the hydrogen transfer to give a ruthenium amine complex.

Casey and co-workers recently proposed a modified outer-sphere mechanism for the reaction of complex **2** with imines (Scheme 13).[15,16] In this refined mechanism, there is an additional intermediate **X** (**X′**) which has a hydrogen bond between NH of the newly formed amine and the carbonyl group of the dienone complexed to ruthenium. The rate-determining step in this mechanism was proposed to vary with the structure and electronic properties of the imine to account for changes in isotope effects. For an *N*-C_6F_5 aldimine significant RuD and OD isotope effects were observed and rate-limiting simultaneous transfer of both RuH and OH was suggested as was proposed earlier for benzaldehyde. For *N*-alkyl aldimines, RuD and OD inverse isotope effects were observed and the rate-limiting step was suggested to be coordination of the hydrogen bonded amine of **X** (**X′**) to Ru; no distinction could be made between a stepwise or concerted transfer of RuH and OH since these transfers occurred before the rate-limiting step.[15] For *N*-aryl aldimines, isotope effects near 1 were observed and it was suggested that the hydrogen transfer and nitrogen coordination steps had similar barriers. When the reduction of an imine by **2′** was carried out in the presence of an added amine, no

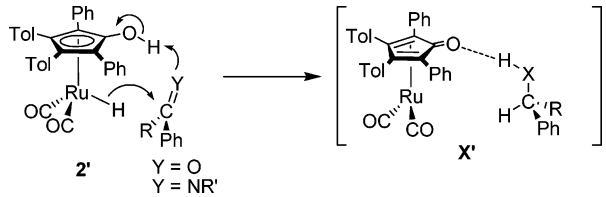
(37) Casey, C. P.; Bikzhanova, G. A.; Bäckvall, J.-E.; Johansson, L.; Park, J.; Kim, Y. H. *Organometallics* **2002**, *21*, 1955.



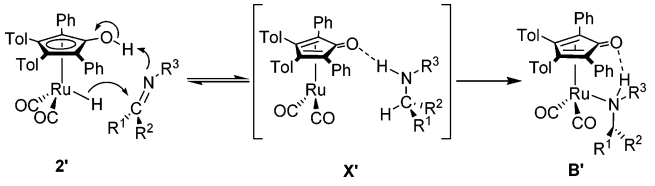
trans-20	*cis*-20
The X-ray crystal data for $C_{50}H_{43}N_2O_3Ru.CH_2Cl_2$ (trans): monoclinic, $P2_1/a$, a= 23.9275(7)Å, b= 14.7281(5)Å, c= 25.8285(7)Å, β= 91.522(2)°, V= 9098.9(5)Å^3, Z=8, Z'=2, T=293(2)K, Docalc= 1.323 g/cm^3, R(int) = 0.0436, R(F) = 0.0583 for 30051 unique reflections. All nonhydrogen atoms were refined with anisotropic displacements parameters. All hydrogen atoms were geometrically positioned and let to ride on their parent atoms with constrained parameters.	The X-ray crystal data for $C_{50}H_{43}N_2O_3Ru.CH_2Cl_2$ (cis): triclinic, P-1, a= 9.723(2)Å, b= 10.737(3)Å, c= 21.644(6)Å, α=100.49(3)° β= 90.74(3)°, γ=98.62(3)°, V= 2194.7(10)Å^3, Z=2, Z'=1, T=293(2)K, Dcalc= 1.371 g/cm^3, R(int) = 0.1323, R(F) = 0.0752 for 8035 unique reflections. All nonhydrogen atoms were refined with anisotropic displacements parameters. All hydrogen atoms were geometrically positioned and let to ride on their parent atoms with constrained parameters.

Figure 1. X-ray structure of the trans and cis isomers of complex **20**.

Scheme 12. Proposed Outer-Sphere Mechanism with Concerted Hydrogen Transfer



Scheme 13. Modified Outer-Sphere Mechanism Proposed for Imines by **2**



products from trapping of unsaturated intermediate **A** by the amine were seen; coordination of nitrogen to ruthenium in **X** (**X′**) was suggested to be more rapid than breaking the hydrogen bond in **X** (**X′**) and diffusion of the new amine and **A** (**A′**) from the solvent cage.[16]

A variant of Casey's proposed concerted mechanisms[13,15] is a stepwise hydrogen transfer in the outer sphere of the metal. Such an ionic mechanism has recently been proposed by Norton and Bullock for the hydrogenation of ketones (aldehydes) and imines by different transition metal hydride catalysts.[38] The metal hydride is suggested to be delivered without prior coordination of the carbon−nitrogen double bond to produce a free amine and an unsaturated catalyst which can combine with the amine to form the amine complex. In the reaction with **2**, the acidic OH would protonate the imine forming the iminium cation. Subsequent hydride addition to the iminium cation followed by coordination of the amine formed would give **B**. Although this two-step outer-sphere mechanism may operate for other hydride catalysts, it does not seem to be involved in the present system (hydride **2** + imines). As is the case for all outer-sphere mechanisms, this mechanism can account for the trapping experiments only if a hydrogen bonded intermediate such as **X** (**X′**) is involved that coordinates nitrogen to ruthenium faster than it breaks apart.

We recently proposed a mechanism based on Shvo's proposal with three different energy barriers; one energy barrier for the coordination of the substrate to ruthenium via ring slippage, another for the hydrogen transfer, and a third for the rearrangement $\eta^2 \rightarrow \eta$.[4] The reaction of **2** with the imine starts with an imine-promoted ring slippage to give intermediate **C** (Scheme 14). This step may or may not be an equilibrium depending on the imine employed. The hydrogen is transferred in a fast step generating η^2-complex **D**, which finally rearranges to η^4-complex **B**.

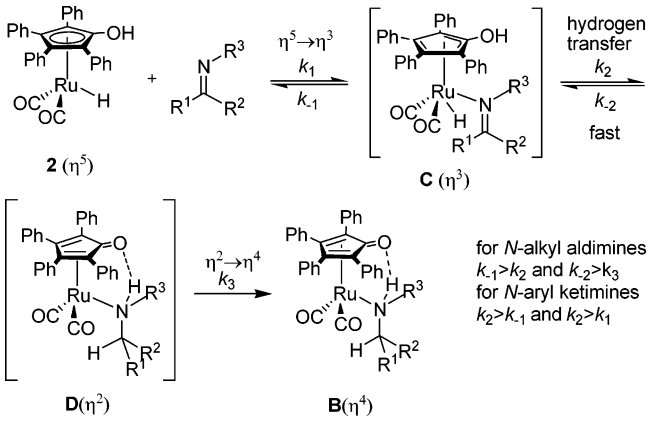
Our group has recently found that a pentaphenylcyclopentadienylruthenium catalyst **22**, lacking the bifunctionality of catalyst **2**, rapidly racemizes secondary alcohols at room temperature (Scheme 15). Thus, (*S*)-1-phenylethanol was racemized within 10 min using 0.5 mol % of **22**.[39] It was demonstrated that there was no exchange with an externally added ketone,[39a] which rules out the formation of a free ketone in the racemization and strongly supports an η^3-hydride ketone intermediate **23**. Thus, there is precedence for the ring slip proposed in Scheme 14.

The phenyl groups on the cyclopentadienyl ring (cf. **22**) are important for the activity since the corresponding $CpRu(CO)_2$-

(38) (a) Guan, H.; Iimura, M.; Magee, M. P.; Norton, J. R.; Zhu, G. *J. Am. Chem. Soc.* **2005**, *127*, 7805. (b) Magee, M. P.; Norton, J. R. *J. Am. Chem. Soc.* **2001**, *123*, 1778. (c) Bullock, R. M. *Chem.—Eur. J.* **2004**, *10*, 2366. (d) Bullock R. M. Ionic Hydrogenations. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Eds.; Elsevier, C. J.: *in press* (ISBN 3-527-31161-0).

(39) (a) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 8817. (b) Csjernyik, G.; Bogár, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **2004**, *45*, 6799.

Scheme 14. Proposed Inner-Sphere Mechanism for Hydrogenation of Imines by **2**



(alkoxide) was very slow in catalyzing the racemization reaction. This suggests that there is a stabilization of the η^3 complex by the phenyl groups similar to that observed with indenyl ligands. It has been reported by Crabtree[40] that a phenyl group on a cyclopentadienyl ligand in an iridium complex may promote ring slip. Whereas $(C_5H_5)IrHL_2$ was unreactive to ligand exchange, $(C_5H_4Ph)IrHL_2$ behaved more like the indenyl analogue and exchanged ligands.[40]

Isotope Effects. The results from the study on kinetic isotope effects in the reduction of *N*-aryl ketimine **12** by **2** support a mechanism where the hydrogen transfer is not rate-determining. The negligible isotope effect found for the hydrogenation of this imine (1.05) cannot be explained with the concerted mechanism originally proposed for the reduction of benzaldehyde by Casey and co-workers.[13] However, in the modified mechanism for imine reduction proposed by Casey,[15,16] this low isotope effect is adequately explained by invoking a reversible hydrogen transfer step (Scheme 13). For *N*-alkyl aldimines inverse kinetic isotopes were observed and explained in terms of rapid fast and reversible hydrogen transfer and rate-determining nitrogen coordination.[15] Negligible isotope effects were observed for *N*-aryl aldimines and explained in terms of comparable rates of hydrogen transfer and nitrogen coordination.[15] Similar arguments can be used to explain the isotope effects in the context of a stepwise outer-sphere ionic mechanism.

The kinetic isotope effects found in the hydrogenation of imine **12** by **2** are adequately explained by the inner-sphere mechanism proposed in Scheme 14. The absence of an isotope effect in the hydrogenation of ketimine **12** by **2** is explained if imine coordination concurrent with ring slippage is slow compared with the hydrogen transfer ($k_2 > k_1$); this amounts to an irreversible rate-limiting coordination step for ketimine **12**. For electron-deficient *N*-C_6F_5 aldimine, the significant RuD and OD isotope effects observed by Casey[15] can be explained in terms of an inner sphere mechanism if the rate-determining step changes from imine coordination to a slow transfer of hydrogen (i.e., k_2 decreases and k_{-1} increases so that k_2 becomes less than k_{-1}, Scheme 14). This decrease of the rate in the hydrogen transfer step (k_2) would be due to less favorable proton transfer to the less basic nitrogen, which would slow the simultaneous transfer of hydrogen from oxygen to nitrogen and from ruthenium to carbon. In this way hydrogen transfer would become rate-determining.

For more electron-rich aldimines (N-alkyl aldimines), the inverse RuD and OD isotope effects observed by Casey[15] can be explained in terms of an inner-sphere mechanism if both imine coordination and hydrogen transfer are fast and reversible and the final η^2- to η^4-conversion becomes rate-limiting. The key factor is probably the very rapid back hydrogen transfer from carbon to ruthenium of the more electron-rich amine; the increase in the rate of this β-elimination is suggested to become large enough to exceed the rate of η^2- to η^4-ring slippage ($k_{-2} > k_3$). In this case the rate-limiting step would be ring slippage from **D** → **B** (Scheme 14). The rate of imine coordination of the more basic N-alkyl aldimines is expected to be faster than that for less electron-rich imines, and the equilibrium formation of an η^3-complex to an electron-rich imine is expected to be more favorable than that for a less electron-rich imine; this would help to explain the faster reaction of electron-rich imines. However, the expected slower hydride transfer to very electron-rich imines than to electron-poor imines is suggested to result in rapid reversible formation of η^3-imine complex **C** ($k_{-1} > k_2$).

A significant CH/CD isotope effect and a negligible NH/ND isotope effect in the dehydrogenation of amine **4** by **2** and 2,6-dimethoxybenzoquinone can only be explained by a two-step mechanism in which C−H bond cleavage alone is rate-determining. Stepwise mechanisms could occur via either outer-sphere or inner-sphere mechanisms (Scheme 16).

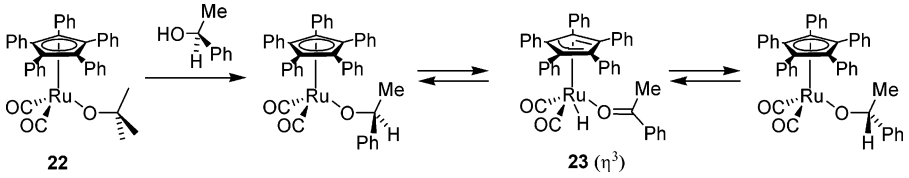
In the outer-sphere mechanism, the transition state for the rate-determining step would involve hydrogen transfer from carbon to ruthenium and little perturbation of the NH bond in going from complex **X** to **Y** in which a protonated imine is hydrogen bonded to the anion formed by deprotonation of the OH of **2**. In the inner-sphere mechanism, the transition state for the rate-determining step would also involve hydrogen transfer from carbon to ruthenium and little perturbation of the NH bond in going from complex η^2 to complex **G** in which a protonated imine is π-bonded to an η^3-cyclopentadienyl.

Attempted Trapping Studies. There are five key trapping experiments that must be explained by imine reduction mechanisms; severe constraints are required to explain all five experiments in terms of either outer-sphere or inner-sphere mechanisms. (1) The absence of intermolecular amine trapping products in Casey's reduction of both N-alkyl and N-aryl aldimines by **2′** and (2) in our reduction of N-alkyl ketimine **14** by **2** under a H_2 atmosphere is readily explained by an inner sphere mechanism starting with imine coordination. (3) Similarly, the absence of intramolecular trapping in the reduction of our amino substituted N-aryl ketimine **18** is readily explained by an inner-sphere mechanism. Explanations of (1−3) in terms of an outer-sphere mechanism require severe constraints. (4) However, the 10% of an intermolecular amine trapping product when the reduction of **14** by **2** was carried out in the absence of hydrogen and (5) the formation of 50% intramolecular amine trapping in the reduction of Casey's amino substituted N-aryl aldimine by **2′** are readily explained by an outer-sphere mechanism. Explanations in terms of an inner-sphere mechanism require severe constraints.

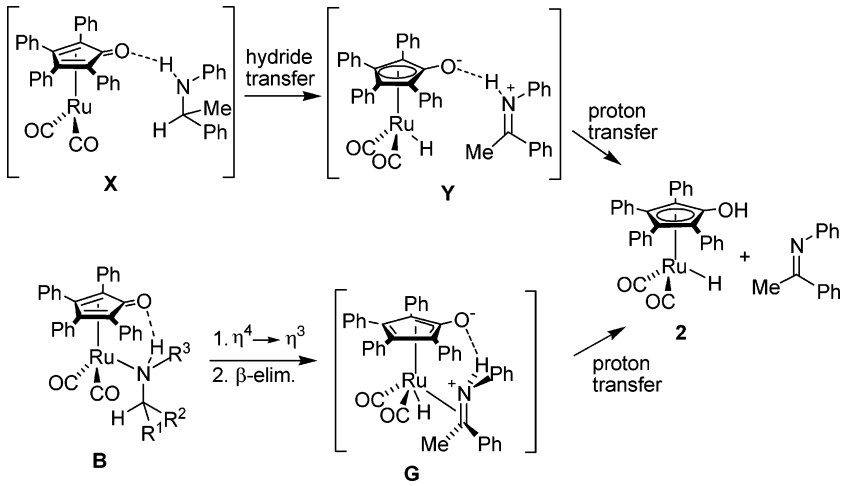
Casey has suggested that the failure to see intermolecular amine trapping was due to initial formation of hydrogen-bonded

(40) Habib, A.; Tanke, R. S.; Holt, E. M.; Crabtree, R. H. *Organometallics* **1989**, *8*, 1225.

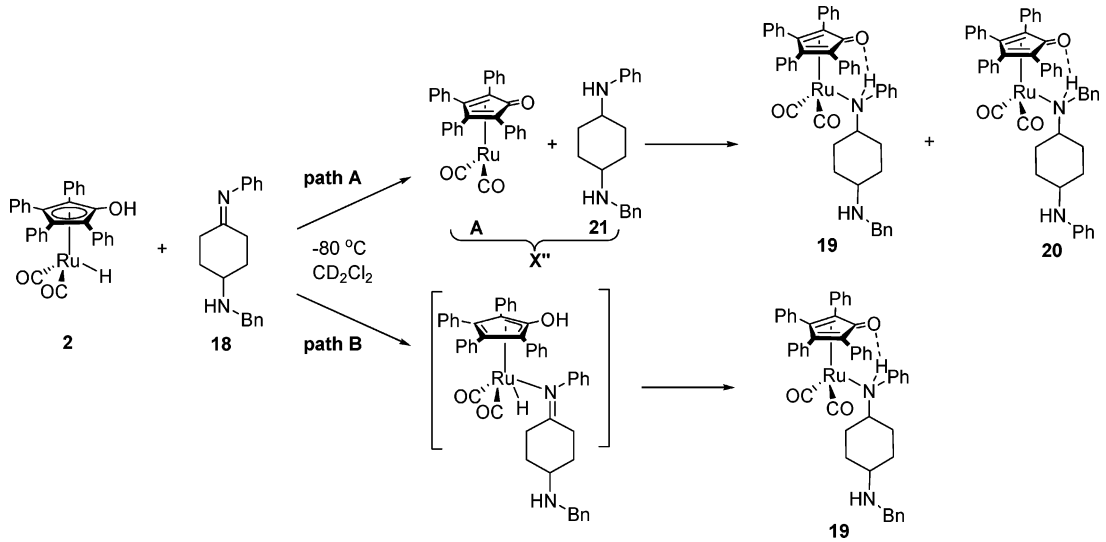
Scheme 15. Racemization of *sec*-Alcohols with an $\eta^5 \rightarrow \eta^3$ Ring Slip



Scheme 16. Possible Two-Step Pathways in Dehydrogenation of Amine



Scheme 17



amine complex **X** (**X′**) where the amine would coordinate to ruthenium much more rapidly than the hydrogen bond was broken with release of the amine from the solvent cage. This would account for observation (1) and (2). Casey explained (5), his observation of an intramolecular trapping product, in terms of formation and breaking the hydrogen bond between the amine and dienone unit of **X″** to generate the new diamine and unsaturated ruthenium species **A** inside a solvent cage; either of the amino groups of the diamine could then hydrogen bond to the dienone and then collapse to two different amine complexes before diffusion from the solvent cage. The failure to see (3), intramolecular trapping in the reduction of *N*-aryl ketimine **18** by **2**, is difficult to explain with the outer-sphere mechanism, and one would have ascribed this to a more rapid coordination of nitrogen than cleavage of the hydrogen bond in **X″** for some not understood reason. The observation of (4), intermolecular trapping in the absence of H_2, might be explained in terms of the outer-sphere mechanism if some dissociation of **X** and diffusion from the solvent cage led to the formation of about 10% trappable intermediate **A**. In the absence of H_2, the external amine could trap **A**, but, in the presence of H_2, **A** might be selectively trapped by H_2 before reaction with the added amine can occur.Observations (1−3) provide strong support for an inner-sphere mechanism. The 50% intramolecular amine trapping (5) observed by Casey occurred with a substrate in which the two amino groups were linked by an arene ring. We suggest that the intramolecular trapping is better explained by ruthenium migration via the aromatic system from one nitrogen to the other in the η^2-cyclopentadienone complex **D** (Scheme 14) prior to η^2- to η^4-ring slippage of the cyclopentadienone to give the amine products. The observation of 10% intermolecular trapping product in the absence of H_2 (4) is ascribed to the

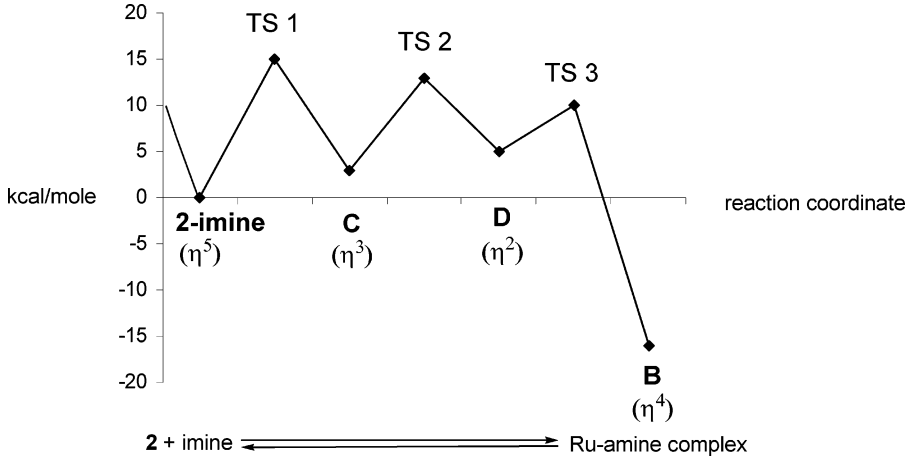


Figure 2. Energy of transition states and intermediates for the transformation of **2** + imine to **B**. The full complex 2,3,4,5-$Ph_4(\eta^5\text{-}C_4COH)Ru(CO)_2H$ (**2**) and imine $Me_2C{=}NMe$ were used.[42]

generation of an unsaturated intermediate (possibly **A**). This could occur via dissociation of amine in the η^2-cyclopentadienone complex **D** (Scheme 14).

Calculations. The modified concerted outer-sphere mechanism was recently supported by calculations.[16] However, in these calculations the solvent effect was not taken into account in either the search for a transition state or in the optimized transition state.[41] Experimentally, it has been found that the hydrogen transfer reactions involving **2** are very solvent dependent. For example, in both the stoichiometric hydrogenations of benzaldehyde[13] and in the catalytic transfer hydrogenation of imines,[8] small amounts of water were added to stabilize the system. Therefore, all intermediates along the reaction coordinate and more importantly all putative transition states should be optimized under more authentic conditions. For example, the search for the transition state could be directly within the continuum solvent model. Interestingly, calculations using such models, where both large numbers of explicit solvent molecules and/or bulk solvent are included, give a quite different picture of the reaction mechanism compared to the gas-phase models. *When the solvent is included, the transition state in the gas-phase models for the concerted mechanism is not located. However, the computations locate defined transition states for the inner-sphere pathway involving coordination of the imine to the ruthenium prior to the hydrogen transfer.*[42] The reaction cycle starts with the imine forming a hydrogen-bonded intermediate with the OH of complex **2**. Such a starting point was also used in the previous calculation.[16] This hydrogen-bonded intermediate (**2-imine**) is designated 0 kcal in the energy diagram (Figure 2). In the calculations, the highest energy barrier is for the conversion of **2-imine** to the η^3 complex **C**, in which the imine is σ-bonded to ruthenium. The ring slippage and nitrogen coordination occur in a single step without intervention of an intermediate. Also, an additional energy barrier very close in energy is located for the hydrogen transfer (TS 2). The hydrogen transfer produces the η^2 complex **D** that finally rearranges to η^4 complex **B** via a third energy barrier, which is the lowest of the three (TS 3). Because of similar energies for the three activation barriers, it is likely that changes in electronic properties of the substrate might change the relative energies of the three transition states. Thus, it is possible that the rate-determining step might change from coordination either to hydrogen transfer or to $\eta^2 \rightarrow \eta^4$ ring slippage for different substrates.

***trans*-Addition of Deuterium.** Casey recently reported that hydrogen transfer from **2′-d₂** (Ru−D, O−D) to imines to give amine complexes was predominantly trans stereospecific, but significant amounts of cis addition was also seen.[43] As discussed by Casey, the inner-sphere mechanism via coordination of the imine would give trans addition exclusively, since ruthenium and hydride would add cis to the imine double bond and the proton would protonate the lone pair of the nitrogen. It is difficult to predict the stereochemistry of imine reduction with a concerted outer-sphere mechanism since the stereochemistry depends on the orientation of the newly generated nitrogen lone pair. The observed preference for trans addition was attributed to steric effects in which the substituents on nitrogen move away from the crowded Cp ring and the new lone pair is directed syn to the newly formed C−H bond and a trans addition results. For the outer-sphere mechanism one has to assume that coordination of the amine occurs faster than nitrogen inversion (cf. Scheme 8, path A), which was proposed by Casey.[43] For the inner-sphere mechanism, the formation of the significant amounts of cis products might be attributed to isomerization of the product upon inadvertent warming of the samples.

Conclusions

We have found substrate effects where electron-rich imines give higher reaction rates than electron-deficient ones in various catalytic hydrogen transfer reactions. In the formation of ruthenium amine complexes the electronic properties of the imine correlate with the temperature at which the formation of amine complex begins. Electron-rich imines form amine complexes with hydride **2** at lower temperatures than electron-deficient imines. Furthermore, the absence of kinetic isotope effects in the hydrogen transfer from **2** to a ketimine excludes a rate-determining hydrogen transfer in contrast to the reaction

(41) For some of the intermediate structures, but not the TS. One single THF molecule was added.
(42) The calculations will be presented in a separate paper: Privalov, T.; Samec, J. S. M.; Bäckvall, J. E. Submitted for publication.
(43) Hydrogen was found to be predominantly trans to the imine (see also refs 15 and 16): Casey, C. P.; Bikzhanova, G. A.; Guzei, I. A. *J. Am. Chem. Soc.* **2006**, *128*, 2286.

with ketones (aldehydes). The kinetic isotope effects observed in the transfer dehydrogenation of an amine clearly show that the hydride transfer alone is rate-limiting, which requires a stepwise mechanism. Exchange studies performed with both an external amine trap (in the presence of H_2) and an internal amine trap are consistent with an inner-sphere mechanism where the substrate is coordinated to the ruthenium prior to hydrogen transfer. The employment of an internal amine trap gave only the ruthenium complex with the amine originating from the imine at low temperatures. An outer-sphere mechanism can explain this result only by assuming that the hydrogen bonded intermediate **X″** (between **A** and diamine **21**) coordinates nitrogen to ruthenium before the hydrogen bond is broken and the diamine can reorient in the solvent cage. Since we view this assumption as highly improbable, we favor an inner-sphere mechanism where the imine coordinates to ruthenium via an $\eta^5 \rightarrow \eta^3$ ring slippage. We believe this mechanism is consistent with all experimental data concerning the reactions of **2** with imines. Computations at a high level are also consistent with the proposed mechanism.

The results presented provide strong support for an inner-sphere process via coordination of the substrate in the transfer hydrogenation of imines and transfer dehydrogenation of amines with the monomers **2** and **A** of Shvo's catalyst **1**, respectively.

Experimental Section

[2,3,4,5-Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_2$NH(Ph)(CHCH$_3$Ph) (9). Imine **8** (0.1 mL, 0.03 mmol, 0.3 M in CD_2Cl_2) was added to a solution of **2** (0.5 mL, 0.06 mmol, 0.12 M in CD_2Cl_2) at −196 °C. The NMR tube was inserted to a precooled spectrometer (−50 °C). The temperature was increased to −40 °C, and at this temperature complex **9** started to form as a mixture of diastereoisomers. After 3 h the conversion to **9** was determined to be 75% by integrating the doublets at δ 0.86 and 1.49 for complex **9** and the singlet at δ 2.2 for imine **8**. ^{1}H NMR (CD_2Cl_2, 400 MHz) major isomer: δ 0.86 (d, J = 6.4 Hz, 3H), 3.46 (d, J = 11.0 Hz, 1H), 4.47 (dq, J = 6.4, 11 Hz, 1H), 5.62 (m, 1H), 5.98 (m, 1H); the other aromatic resonances were obscured by **2**. Minor isomer: 1.49 (d, J = 8.3 Hz, 3H), 4.32 (brd, J = 7.1 Hz, 1H), 4.49 (m, 1H); the other resonances were obscured by the other isomer and **2**. ^{13}C NMR (100 Hz, CD_2Cl_2, −35°C) major isomer: δ 24.3, 25.4, 83.7, 85.9, 102.2, 104.7, 113.1, 119.5, 123−133 (21 resonances), 141.0, 162.0, 199.3, 201.6. Minor isomer: δ 27.1, 53.4, 82.4, 87.8, 102.3, 103.6, 117.1; all other resonances were too weak or obscured by the other isomer or **2**. The spectrometer was heated to −30 °C where the free amine appeared with a characteristic resonance at δ 1.47 (d, J = 6.4 Hz).

[2,3,4,5-Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_2$NH(Ph)(CHCH$_3$Ph-*p*-MeO) (13). Imine **12** (0.1 mL, 0.03 mmol, 0.3 M in CD_2Cl_2) was added to a solution of **2** (0.5 mL, 0.04 mmol, 0.08 M in CD_2Cl_2) at −196 °C. The NMR tube was inserted into a precooled spectrometer (−60 °C), and the temperature increased to −58 °C where the complex appeared as a 3:1 mixture of diastereomers. The conversion to complex **13** was 56% after 3 h of integrating the singlets at δ 3.58 and 3.62 for complex **13** and the singlet at δ 3.85 for imine **12**. ^{1}H NMR (CD_2Cl_2, 400 MHz, −35 °C) of the major isomer: δ 0.82 (d, J = 6.4 Hz, 3H), 3.35 (d, J = 11.0 Hz, 1H), 3.58 (s, 3H), 4.49 (dq, J = 11.0, 6.4 Hz, 1H), 5.57 (m, 1H), 5.98 (m, 1H). All other resonances were obscured by **2**. Minor isomer: δ 1.46 (d, J = 8.3 Hz, 3H), 3.62 (s, 3H), 4.06 (m, CH). All other resonances were obscured by the major isomer and **2**. ^{13}C NMR (100 Hz, CD_2Cl_2, −35 °C) major isomer: δ 24.3, 55.2, 67.5, 83.7, 85.8, 102.2, 104.7, 113.4, 124−133 (22 resonances), 150.6, 158.4, 199.4, 201.6. Minor isomer: δ 25.4, 67.2, 83.1, 85.6, 102.3, 103.6; the other resonances were too weak or obscured by the other isomer or **2**. The spectrometer was then heated to −25 °C where the free amine appeared with characteristic resonances at δ 1.44 (d, J = 8.3 Hz, 3H), 3.75 (s, 3H).

[2,3,4,5-Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_2$NH(CH$_3$)(CHCH$_3$Ph) (15). Imine **14** (0.1 mL, 0.03 mmol, 0.3 M in CD_2Cl_2) was added to a solution of **2** (0.5 mL, 0.04 mmol, 0.08 M in CD_2Cl_2) at −196 °C. The NMR tube was inserted to a precooled spectrometer (−90 °C), and the complex appeared as diastereomers in total conversion. The solvent was then evaporated, C_6D_6 (0.6 mL) was added, and the spectrometer was gradually heated to 47 °C at which temperature the complex decomposed. The two diastereomers were also synthesized according to a literature procedure[13] and separated by column chromatography using CH_2Cl_2/pentane. ^{1}H NMR (400 Hz, $CDCl_3$, 25°C) major isomer: δ 1.56 (d, J = 7.3 Hz, 3H), 2.07 (d, J = 5.5 Hz, 3H), 3.88 (m, J = 5.5, 7.3 Hz, 1H), 6.86 (m, 4H), 7.11 (m, 18H), 7.55 (m, 2H), 7.75 (m, 1H). ^{13}C NMR (100 Hz, $CDCl_3$, 25°C) δ 14.9, 38.0, 65.5, 83.3, 83.8, 102.9, 104.5, 126.4−139.3 (20 resonances), 163.6, 200.8, 201.5. IR ($CDCl_3$): ν = 2004, 1946, 1600, 1578, 1567, 1499, 1446 cm^{-1}. HRMS (ES+) (M + H)$^+$ calcd for $C_{40}H_{33}NO_3Ru$, 677.1504; found, 677.1496. ^{1}H NMR (400 Hz, $CDCl_3$, 25°C) minor isomer: δ 0.90 (d, J = 6.8 Hz, 3H) 2.15 (d, J = 5.9 Hz, 3H), 3.70 (m, 1H), 7.10 (m, 23H), 7.62 (m, 2H). ^{13}C NMR (100 Hz, $CDCl_3$, 25°C) δ 23.4, 46.6, 68.5, 83.7, 84.0, 103.4, 105.1, 126.2−141.4 (20 resonances), 162.4, 200.7, 201.4. IR ($CDCl_3$): ν = 2005, 1948, 1600, 1577, 1562, 1499, 1446 cm^{-1}. HRMS (ES+) (M + H)$^+$ calcd for $C_{40}H_{33}NO_3Ru$, 677.1504; found, 677.1492.

Kinetic Isotope Study: Stoichiometric Hydrogenation. Complex **2** and **2-d$_2$** were prepared from **3** and H_2 or D_2, respectively, as described in the Supporting Information. The THF was evaporated, and CD_2Cl_2 saturated with H_2O or D_2O (depending on whether **2** or **2-d$_2$** was used) was added. The solution of **2** (0.50 mL of a 2 M solution, 0.10 mmol) was syringed into an NMR tube under an argon atmosphere and cooled to −196 °C. Freshly distilled imine **12** (0.100 mL of a 0.04 M solution in CD_2Cl_2, 4 μmol) was added by syringe to the NMR tube, and the mixture was warmed to −78 °C and carefully shaken. The NMR tube was recooled to −196 °C and put into the spectrometer precooled to −65 °C. At this temperature, no reaction occurred and the sample was initially locked and shimmed, and an acquisition was run to double-check the concentrations (that pseudo-first-order kinetics was followed) and that no reaction had taken place. The temperature was set to −54 °C, the sample was shimmed, and t_0 was set when the temperature had reached −54 °C. The time between when the temperature was initially set to −54 °C and the first acquired spectrum was ∼140 s (reactions that had proceeded more than 25% were discarded). The reaction was followed until at least 2 half lives (24 min), integrating the methoxy peaks of **12** and free imine.

Kinetic Isotope Study: Catalytic Transfer Dehydrogenation. An NMR tube was charged with 2,6-dimethoxy-1,4-benzoquinone (11.2 mg, 0.07 mmol) under argon. The amine **4** was added by syringe (0.3 mL, 0.026 mmol, 0.086 M in toluene-d_8). The NMR tube was inserted into a prewarmed spectrometer (100 °C) for 5 min to dissolve the quinone. The NMR tube was ejected, and complex **1** was added by syringe (0.45 mL, 2.16 μmol, 4.85 mM in toluene-d_8) and the NMR tube was reinserted into the spectrometer. The reactions were followed at 100 °C until at least 2 half lives, integrating the signals for the amine (δ 1.15−1.23) and the imine (δ 1.84−1.92) using ferrocene as internal standard. The first 10% conversion was not taken into consideration in obtaining the rate as catalyst **1** took a few minutes to completely dissociate.

Exchange Study with External Amine Trap. Complex **2** (55 mg, 0.1 mmol) dissolved in CD_2Cl_2 (0.4 mL), and the 0.25 M solution of **2** was added by syringe into an NMR tube under Ar and cooled to −196 °C. Freshly distilled **16** (0.5, 1, or 2 mmol; 0.5, 1, or 2 M; 0.1 mL of CD_2Cl_2) and **14** (0.1 mmol, 1 M, 0.1 mL) were added, and the sample was warmed to −78 °C and carefully shaken. The sample was

put into a spectrometer precooled to −20 °C, and the reaction was analyzed by ^{1}H NMR integrating the doublets at δ 0.88 for **17** and at δ 0.93 for **15**.

[2,3,4,5-Ph$_4$(η_4-C$_4$CO)]Ru(CO)$_2$NH(CH$_3$)(CH(4-MeO−Ph)-(CH$_3$)) (17). The title compound was independently synthesized by a literature procedure[13] adding amine **16** (66 mg, 0.4 mmol) to a suspension of **3** (0.24 g, 0.2 mmol) in CH_2Cl_2 (1 mL). Complex **17** was precipitated from CH_2Cl_2/hexanes. Yield (0.17 g, 60%) of yellow crystals. Both diastereomers were separated by column chromatography using CH_2Cl_2. ^{1}H NMR (400 Hz,$CDCl_3$, 25 °C) major isomer: δ 1.53 (d, J = 7.1 Hz, 3H), 2.06 (d, J = 5.7 Hz, 3H), 3.74 (s, 3H), 3.85(q, J = 7.1, 1H), 6.70−6.78 (m, 4H), 7.0−7.24 (m, 16H), 7.55−7.57 (m, 2H), 7.73−7.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 15.0, 37.8, 55.4, 65.1, 83.3, 83.7, 102.9, 104.4, 126.3−132.7 (19 resonances), 159.5, 163.6 200.8, 201.6. IR ($CDCl_3$): ν = 2243, 2005, 1946, 1601, 1578, 1566, 1500, 1446 cm^{-1}. HRMS (ES+) (M + H)$^+$ calcd for $C_{41}H_{35}NO_4Ru$, 707.1610; found, 707.1608. ^{1}H NMR (400 MHz,$CDCl_3$, 25 °C) minor isomer: δ 0.95 (d, J = 6.7 Hz, 3H), 2.17 (d, J = 5.8, 3H), 3.62−3.73 (m, 1H), 3.73 (s, 3H), 6.67−6.78 (m, 2H), 6.97−7.29 (m, 18H), 7.51−7.65 (m, 2H), 7.70−7.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 22.7, 46.5, 55.3, 67.5, 83.6, 84.0, 103.3, 105.0, 114.0, 114.2, 126.1−133.2 (17 resonances), 159.2, 162.4, 200.8, 201.5. IR ($CDCl_3$): ν = 2237, 2006, 1948, 1601, 1578, 1566, 1500, 1446 cm^{-1}. HRMS (ES+) (M + H)$^+$ calcd for $C_{41}H_{35}NO_4Ru$, 707.1610; found, 707.1598.

Internal Trapping Experiment. Hydrogenation of Imine 18 by 2. Imine **18** (100 μL, 0.74 M, 74 μmol) was added to **2** (0.5 mL, 0.15 M, 74 μmol) at −196 °C in an NMR tube. The NMR tube was inserted into a precooled spectrometer (−90 °C). The temperature was set to −80 °C, and at this temperature the resonances from the imine broadened and complex **19** started to form and appeared as diastereomers. At this temperature only two benzylic singlets with ^{1}H NMR resonances at ∼δ 3.5 were distinguishable due to broadening. There was full conversion to complex **19** within 20 min. The reaction was monitored by integrating the new signal at δ 3.5 (complex **19**), the signal at δ 3.75 (imine **18**), and that at δ −9.85 (complex **2**). Complex **19** was stable to −8 °C where complex **20** appeared. At −8 °C complex **19** still dominated the spectrum, and only traces (<5%) of complex **20** were visible. The NMR spectrum of **19** is difficult to assign since it appears as a mixture of diastereoisomers. ^{1}H NMR (400 MHz, CD_2Cl_2, −8 °C) from the mixture of diastereomers (∼1:1): δ 0.32 (m, 0.5 H), 0.77 (m, 1H), 1.27 (m, 2.5H), 1.92 (m, 2H), 2.06 (m, 1H), 2.29 (m, 1H), 2.50 (m, 0.5 H), 2.76 (brd, J = 11 Hz, 0.5H), 3.02 (brs, 0.5H), 3.41 (brs, 0.5H), 3.51 (s, 1H), 3.53 (s, 1H) 6.61 (m, 0.5H), 6.76 (m, 0.5H), 7.16 (m, 23H), 7.63 (m, 1H).

The experiment with ^{15}N labeled imine **18** was carried out as described above. ^{15}N NMR (40 MHz, CD_2Cl_2, −20 °C) δ −296 (complex **19**); ^{15}N NMR (40 MHz, CD_2Cl_2, 25 °C) δ −294 and −304 (complex **20**).

[2,3,4,5-Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_2$NH(Bn)(C$_6$H$_{10}$-*p*-*N*Ph) (20). The title compound was made according to a literature procedure using complex **3** (50 mg, 46 μmol) and amine **21** (60 mg, 200 μmol).[13] Yield: (21 mg, 55%) of yellow crystals. Both diastereomers were separated by column chromatography using CH_2Cl_2/pentane. Single crystals were grown in CH_2Cl_2/hexane at −20 °C. ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C) *cis*-**20**: δ 0.22 (m, 1H), 0.86 (ddd, J = 13.6, 9.9, 3.9 Hz, 1H), 1.06 (dd, J = 13.6, 7.3, 3.7 Hz, 1H), 1.23 (m, 1H), 1.44 (m, 1H), 1.93 (m, 2H), 2.05 (brd, J = 11.5 Hz, 1H), 2.14 (brt, J = 10.8 Hz, 1H), 3.45 (d, J = 2.8 Hz, 1H), 3.57 (dd, J = 13.6, 2.8 Hz, 1H), 3.68 (brd, J = 7.8 Hz, 1H), 3.85 (dd, J = 13.6, 11.7 Hz, 1H), 6.47 (m, 2H), 6.63 (m, 1H), 7.13 (m, 23H), 7.68 (m, 4H). ^{13}C NMR (100 MHz, CD_2Cl_2, 25°C) δ 25.1, 27.3, 28.0, 28.3, 46.2, 57.6, 60.6, 80.9, 85.1, 104.3, 104.7, 113.5, 117.2, 126.6−138.0 (21 resonances), 147.5, 163.7, 201.0, 204.0. ^{15}N NMR (40 MHz, CD_2Cl_2, 25 °C) δ −304. IR (CD_2Cl_2): ν = 3087, 3056, 2939, 2862, 2002, 1945, 1601, 1577, 1564, 1499, 1466 cm^{-1}. HRMS (ES+) (M + H)$^+$ calcd for $C_{50}H_{44}N_2O_3Ru$, 822.2395; found, 822.2409. ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C) *trans*-**20**: δ 0.45 (m, 1H), 0.65 (m, 1H), 0.9 (m, 2H), 1.44 (m, 2H), 1.61 (brs, 1H), 2.12, (m, 4H), 3.03 (m, 1H), 3.29 (brs, 1H), 3.58 (dd, J = 13.6, 2.6 Hz, 1H), 3.82 (dd, 13.6, 11.7 Hz, 1H), 6.48 (m, 2H), 6.62 (m, 1H), 7.19 (m, 23H), 7.70 (m, 4H). ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C) δ 29.3, 31.6, 31.6, 31.7, 51.7, 57.2, 60.9, 83.3, 84.8, 104.4, 104.5, 113.5, 117.5, 126.7−137.9 (20 resonances), 147.8, 163.6, 201.1, 203.4 (1 carbon is missing in the aromatic region). ^{15}N NMR (40 MHz, CD_2Cl_2, 25 °C) δ −294. IR (CD_2Cl_2): ν = 3086, 3055, 3026, 2929, 2855, 2001, 1941, 1601, 1577, 1565, 1499, 1446. HRMS (ES+) (M + H)$^+$ calcd for $C_{50}H_{44}N_2O_3Ru$, 822.2395; found, 822.2387. Complexes *cis*-**20** and *trans*-**20** were further characterized by their crystal structures (see text and Supporting Information).

Acknowledgment. This work was supported by grants from the Swedish Research Council. Professor Casey and co-workers are gratefully acknowledged for many fruitful discussions. We thank Vincent Lecomte for the alternative route to **9** via **11**.

Supporting Information Available: General methods, experimental procedures for the synthesis of **2**, **14**, **18**, and **21** and for an alternative route to **9**. CIF files for compounds *cis*-**20** and *trans*-**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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