DOI: 10.1002/chem.200801195

# Investigation of a Possible Solvent Cage Effect in the Reduction of 4-Aminocyclohexanone by a Hydroxycyclopentadienyl Ruthenium Hydride

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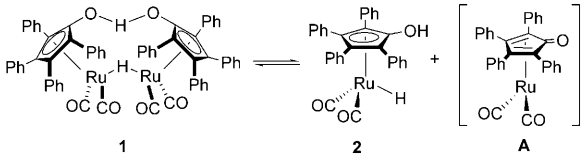
**Abstract:** No solvent cage effect could be found in the reduction of 4-aminocyclohexanone **3** by Shvo's hydroxycyclopentadienyl ruthenium hydride **2**. No preference was observed in the complex formation from trapping by aminoalcohol product **4** over external trapping by aminoketone **3** or by Shvo hydride **2**. A solvent cage effect has previously been proposed to support an outer-sphere mechanism in the reduction of imines by **2**; this was based on the observation that there was >90% preference for complexation of the newly formed amine over an external amine. Since alcohols form stronger hydrogen bonds than amines a larger cage effect would be expected in the present study. The lack of a cage effect in the present reduction suggests that the previous results from imine reduction require an additional explanation (other than a solvent cage effect).

**Keywords:** hydrogenation · reduction · ruthenium · solvent effects

## Introduction

Hydrogen-transfer reactions have emerged as important transformations in organic synthesis over the past two decades.[1] The use of chiral ligands in these reactions have led to useful enantioselective transfer hydrogenations.[1b,2,3] Many of the transition-metal catalysts used for these transfer hydrogenations have also found applications in enantioselective hydrogenation of ketones by $H_2$.[1c,4] These catalysts are often so-called metal–ligand bifunctional catalysts, which transfer hydrogen fast to aldehydes, ketones, and imines. In the hydrogen transfer from these catalysts to a ketone or an imine a hydrogen on the metal adds as a hydride (to carbon) and a hydrogen on the ligand adds as a proton (to the heteroatom).[5] One frequently used metal–ligand bifunctional catalyst is the so-called Shvo catalyst (**1**),[6] which has found applications in hydrogen-transfer reactions[7] and has served as a racemization catalyst in enzyme-based dynamic kinetic resolution.[8] The Shvo catalyst **1** dissociates into **2** and **A** in solution at elevated temperature.




The mechanism of the reduction of aldehydes and ketones by hydride **2** as well as the dehydrogenation of alcohols by complex **A** has been studied.[9,10] In both cases the measured deuterium isotope effects show that the reactions are concerted. In the hydrogenation the OH proton and Ru hydride of **2** are transferred from the catalyst to the substrate at the same time and in the dehydrogenation the O-H and C-H hydrogens of the alcohol are simultaneously transferred to the oxygen and the Ru center of **A**, respectively. These results are best explained by an outer-sphere hydrogen transfer without coordination of the substrate but do not completely rule out coordination followed by concerted transfer of the two hydrogens. However, in the ketone reduction the inner-sphere pathway would require a $\eta^5 \rightarrow \eta^3$ ring slip induced by coordination, which seems less likely. For the reversed reaction, dehydrogenation of the alcohol, coordination of the alcohol most likely occurs in **A** but the subsequent β-elimination would require a $\eta^5 \rightarrow \eta^3$ ring slip.

For the corresponding reduction of imines by Ru hydride **2** and dehydrogenation of amines to imines by coordinatively unsaturated **A**, the question concerning outer-sphere versus inner-sphere hydrogen transfer is still controversial.[11,12] There is a consensus that the imine/amine reactions are different from the corresponding ketone/alcohol reactions. For the former type of reactions a stepwise hydrogen transfer occurs depending on the amine/imine employed.[13]

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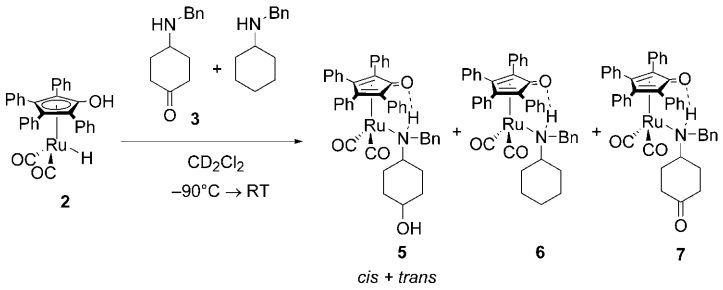
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801195.

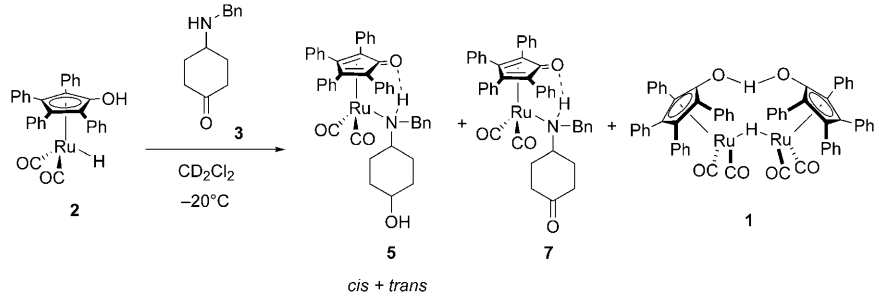
   

In stoichiometric reduction of imines to amines a complex with the coordinated amine product is formed. In the outer-sphere mechanism it was suggested that after delivery of the two hydrogens to the imine, the amine formed would combine with Ru species **A**, while in the inner-sphere pathway the nitrogen is coordinated to ruthenium throughout the reaction. One of the first attempts to distinguish between these two pathways was to use an added amine as an external trap. The imine was reduced by Ru hydride **2** in the presence of the added amine since competition between newly formed amine and added amine trap is expected.[11a,12–14] The failure of the added external amine to form a ruthenium amine complex supports an inner-sphere pathway and would seem to rule out the outer-sphere pathway. However, a solvent cage effect was proposed for the outer-sphere pathway to account for these results.[11,13] In the latter mechanism the newly formed amine would only slowly dissociate out of the cage and subsequent coordination to the metal would be faster than dissociation.

In the present study we have investigated a possible cage effect in the reduction of 4-aminocyclohexanone by Ru hydride **2**. This reduction leads to the ruthenium amine complex of 4-aminocyclohexanol. If the reduced amino alcohol stays in the solvent cage, trapping by an external amine trap would be slow and the amine complex of 4-aminocyclohexanol would predominate. If there were no cage effect, there would be competition between the external amine trap and 4-aminocyclohexanol. Our experiments show that there is no measurable cage effect in the reduction of 4-aminocyclohexanone by **2**.




Scheme 1.




Scheme 2.

## Results

In our studies on a possible solvent cage effect in hydrogenation with **2** we used 4-benzylaminocyclohexanone (**3**) as the substrate. Reaction of this ketoamine would produce 4-(benzylamino)cyclohexanol (**4**), which after coordination to the 16-electron complex **A** would give Ru amine complex **5**. This substrate was chosen since the alcohol moiety does not form a stable coordination complex with Ru[15] and therefore failure of trapping by an external amine in this case would occur only because of a cage effect. With a large cage effect only Ru amine complex **5** would form and neither *N*-cyclohexylbenzylamine nor unreacted **3** would coordinate to ruthenium. Initially we used *N*-cyclohexylbenzylamine as an added amine trap and preliminary experiments showed that amine trapping products **6** and **7** were formed together with Ru amine complex **5** (Scheme 1).

Unfortunately, ruthenium amine complex **6** overlaps with one of the isomers of ruthenium amine complex **5** (the *cis* isomer) in the $^1$H NMR spectrum, which made an accurate analysis difficult. We therefore decided to use only the unreacted aminoketone **3** as the external amine trap (Scheme 2).

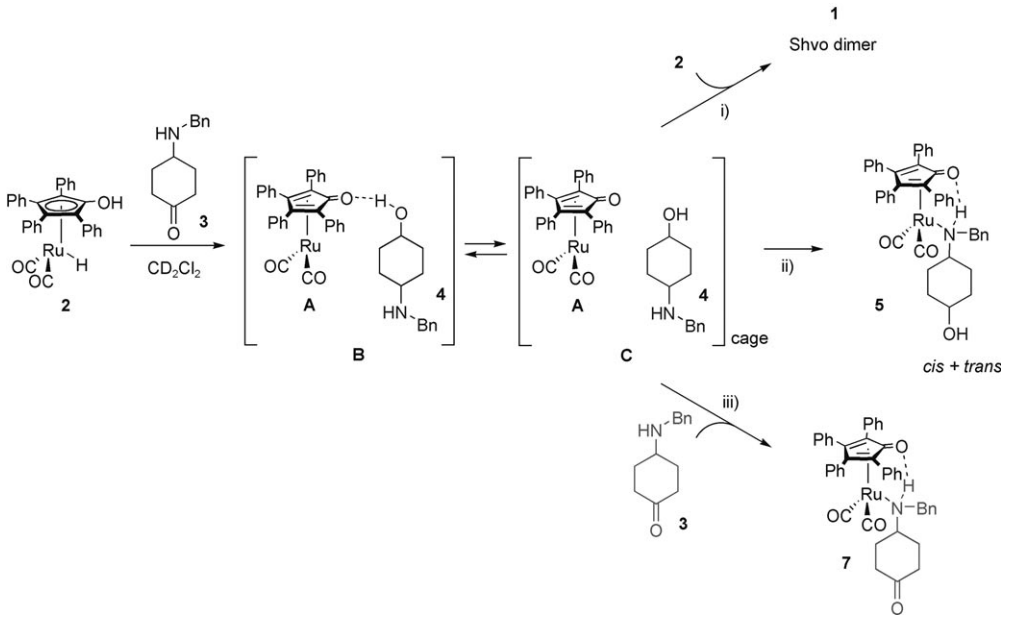
Reaction of hydride **2** with aminoketone **3** in $CD_2Cl_2$ at −20 °C was monitored by $^1$H NMR spectroscopy. Equimolar amounts of ruthenium hydride **2** and aminoketone **3** as solutions in $CD_2Cl_2$ were added to an NMR tube at −196 °C. The components were not mixed at this temperature. The NMR tube was then transferred to the −20 °C pre-cooled probe of the NMR spectrometer and $^1$H NMR spectra were run continuously.

In the reduction of ketones with hydride **2** the 16-electron complex **A** is formed, which in the absence of nucleophiles combines with ruthenium hydride **2** to give Shvo dimer **1**. (cf. Scheme 3). However, in the reaction in Scheme 3 complex **A** can also react with the amine function in the reduced amino alcohol as well as with the amine function of the ketoamine.

Thus the 16-electron complex (**A**) formed in the hydrogen transfer from **2** to the ketone can produce three different products (of which the ratio will depend on the magnitude of the cage effect): i) Shvo dimer **1**, ii) amino alcohol complex **5**, and iii) ketoamine complex **7**. The second product, amino alcohol complex **5**, is formed as a *cis*/*trans* mixture. The formation of all these products as well as the disappearance of hydride **2** was monitored by $^1$H NMR spectroscopy and the results are given in Figure 1.

The NMR analysis in Figure 1 shows that all three products **7**, **5**, and Shvo dimer **1** are formed in the reaction. From




Scheme 3.

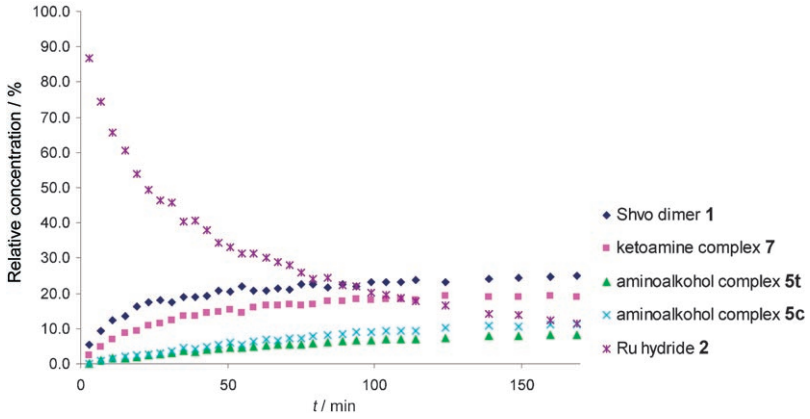



Figure 1. Relative concentration of Ru species over time in the reaction between Ru hydride **2** and aminoketone **3** according to $^1$H NMR.[16] Ru-hydride **2** (0.074 mmol) and aminoketone **3** (0.074 mmol) in $CD_2Cl_2$ were mixed at −196 °C and heated to −20 °C. The reaction was followed by $^1$H NMR at −20 °C.

Figure 1 one can see that after a while about half of the unsaturated complex **A** generated is quenched by hydride **2** to give dimer **1**, and that the other half of **A** has reacted with the amine compounds to give amine complexes **5** and **7**. It is obvious from Figure 1 that there is not a strong cage effect. With a strong cage effect complex **5** would have predominated and no Shvo dimer **1** would have been formed. One could argue that the trapping of **A** by hydride **2** is much more efficient than the reaction of hydride **2** with the newly formed amino alcohol **5**. However, a control experiment showed that **A** reacts with *N*-cyclohexylbenzylamine and hydride **2** with comparable rates.[17] Also the fact that complex **7** is the predominant amine complex supports the absence of a large cage effect. With a large cage effect the ratio **5**/**7** would have been $\gg 1$. As can be seen from Figure 1 ketoamine complex **7** predominates over **5** at the early stage of the reaction, but after a while a larger proportion of amino alcohol complex **5** is formed. From the ratio **5**(*cis*+*trans*)/**7** it is obvious that there cannot be any significant cage effect. In an attempt to quantify a possible small cage effect we calculated the expected ratio **5**(*cis*+*trans*)/**7**[18] (assuming that there is no cage effect) and compared it with the observed ratio **5**(*cis*+*trans*)/**7** (Figure 2). Figure 2a shows that the observed ratio was slightly larger than the calculated ratio and this would seem to indicate that there is a small cage effect of about 1.2–1.7. However, in the calculations of the ratio **5**(*cis*+*trans*)/**7** we have assumed that ketoamine complex **7** is stable and therefore not reduced to amino alcohol complex **5** by **2**. A control experiment, however, showed that this assumption is not correct.[19] Thus, when cyclohexanone and ketoamine complex **5** in a 1:1 ratio was allowed to react with hydride **2** they were reduced with approximately the same rate. The predicted ratio **5**(*cis*+*trans*)/**7** from a non-cage-effect scenario as well as the actual ratio **5**(*cis*+*trans*)/**7** were therefore corrected for the transformation of **7** → **5** during the reaction.[20] The expected ratio **5**(*cis*+*trans*)/**7** corrected for the reduction of **7** → **5** and the observed ratio **5**(*cis*+*trans*)/**7** are given in Figure 2b. As can be seen from Figure 2b the calculated ratio assuming no cage effect and the observed ratio are very similar. From these data we conclude that there is no measurable cage effect in the hydrogen transfer from hydride **2** to ketoamine **3**.

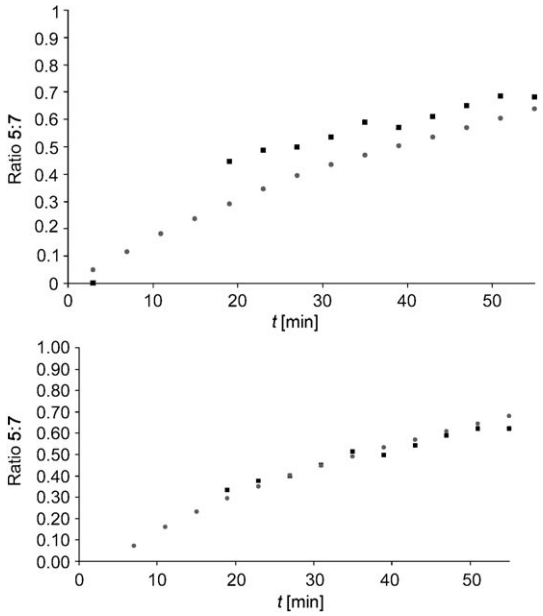
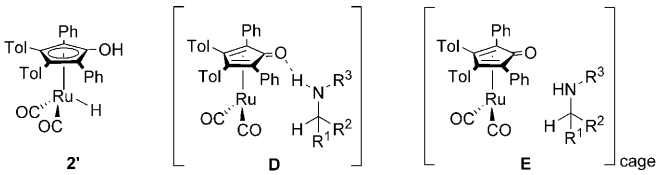



Figure 2. a) Actual (■) and expected (●) ratio between Ru-amine complexes **5** and **7**. b) Corrected actual (■) and expected (●) ratio between Ru-amine complexes **5** and **7**.

## Discussion

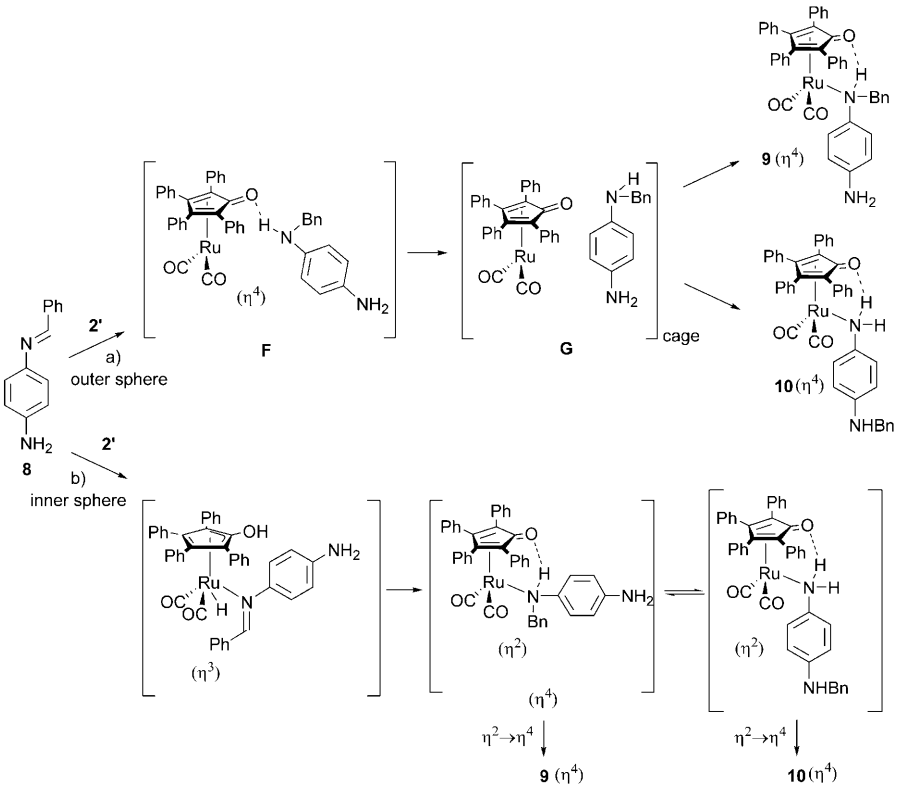
It has been proposed that there is a strong cage effect in hydrogenation of imines by **2′**, where the amine does not easily dissociate out from the cage. This strong cage effect was explained by a hydrogen bonded intermediate **D**, in which there is a hydrogen bond between the newly formed amine and the keto group of complex **A′**. Breakage of the hydrogen bond would give the cage complex **E**.

It was argued that coordination of the amine to give an amine complex was faster than diffusion of the amine from the cage **E**. This would explain why an external amine does not compete with the coordination site at ruthenium.[11a,12–14] Also, it was proposed that when there is another amine function present in cage bound amine, for example, as in **F** and **G**, the diamine stays in the cage (Scheme 4, path a). As a consequence both amine complexes would form due to approximately equal probability of the two amines to coordinate to ruthenium.




Hydrogenation of imine **8** by **2′**, as previously reported by Casey,[11a] afforded a 1:1 mixture of **9** and **10**, which would seem to support the cage hypothesis (Scheme 4, path a). Another explanation for the observed results, proposed by us,[12] is that the reaction occurs via an inner-sphere pathway to give a $\eta^2$-amine complex, which could undergo intramolecular nitrogen exchange via the benzene ring (Scheme 4, path b). This was supported by experiments with an analogous intramolecular amine trap with a cyclohexane linker instead of the benzene linker, which gave only the amine complex of the newly formed amine.[12] Casey has recently shown that in the reduction of imines with some intramolecular amine traps by **2′** a small amount ($\approx$10%) of the amine complex from the trap amine was formed.[11b] This was inferred as support for an outer-sphere pathway.[11b]

The results from the present study seem to be incompatible with the outer-sphere pathway. According to the cage hypothesis a hydrogen-bonded intermediate **B** would be




Scheme 4.

formed in the reduction of aminoketone **3** by **2**. Intermediate **B** would be in equilibrium with **C**.

It is known that alcohols form much stronger hydrogen bonds than amines.[21] Intermediate **B** would therefore show much stronger effect in keeping the hydrogen-bonded molecule in the cage than any of the amine analogues **D** and **F**. If there were a strong cage effect as hypothesized by Casey,[11,13] it is remarkable that there is no observable cage effect with intermediate **C**, which should be formed in the reduction of ketone **3** by Ru hydride **2** after the hydrogen bond is broken.

An alternative interpretation of the results, suggested by one of the referees, is that because of the strong hydrogen bond of the alcohol in **B**, trapping of **A** by ketoamine **3**, free amino alcohol **4** (from outside the cage) and Shvo hydride **2** (to give **1**) could occur while **4** is still hydrogen-bonded. We do not see how trapping of **A** by Shvo hydride **2** could take place in the hydrogen-bonded complex **B** since this trapping requires binding to the carbonyl oxygen of the cyclopentadienyl ring. We consider this alternative mechanism less likely and favor breaking of the hydrogen bond to give "cage complex" **C** in line with previously proposed pathways in the outer-sphere mechanism.[11]

## Conclusion

Our results show that there is no measurable cage effect in the reduction of 4-aminocyclohexanone **3** by Ru hydride **2**. If there were a cage effect, it would be expected to be larger in ketone reduction than imine reduction, since alcohols form stronger hydrogen bonds than amines.[21] Therefore, the failure to observe ruthenium–amine complexes from externally added amine traps in the reduction of imines[11a,12] can not simply be explained by a cage effect.

## Experimental Section

All reactions were performed under dry argon atmosphere in flame-dried glassware. $^1$H and $^{13}$C NMR spectra were recorded at 400 or 500 MHz and at 150 MHz, respectively. Chemical shifts ($\delta$) are reported in ppm, using the residual solvent peak in $CD_2Cl_2$ ($\delta_H$ 5.32 and $\delta_C$ 54.00) or in $CDCl_3$ ($\delta_H$ 7.26) as internal standard. Coupling constants ($J$) are given in Hz. Ru-dimer **1**,[9] Ru hydride **2**,[12] and 4-(benzylamino)cyclohexanone (**3**)[9] were prepared according to literature procedures. Spectral data were in accordance with the literature.

**Reduction of 4-(benzylamino)cyclohexanone (3) by Ru-hydride 2**: A solution of Ru-hydride **2** (0.25 mL, 0.15 M in $CD_2Cl_2$, 0.037 mmol) was added via a syringe into an NMR tube under argon atmosphere. After three freeze–pump–thaw cycles the reaction mixture was frozen to −196 °C. Aminoketone **3** (0.10 mL, 0.74 M, 0.074 mmol) in $CD_2Cl_2$ was added via a cannula to the frozen mixture to ensure that the components did not mix. Additionally Ru-hydride **2** (0.25 mL, 0.15 M in $CD_2Cl_2$, 0.037 mmol) was carefully added in the same way (while frozen). The NMR tube was transferred into the spectrometer which had been precooled to −20 °C and $t_0$ was set when the sample was inserted. At this time and temperature the sample was still frozen (i.e., no field signal could be observed even though the spectrometer indicated that the sample was "down"). Within one minute the reaction mixture started to thaw. After locking and shimming, the reaction was followed by integration of the peaks at $\delta$ 0.55, 0.19, 0.00, −9.70 and −17.42 ppm corresponding to Ru-amine complexes **7**, *trans*-**5**, *cis*-**5**, Ru-hydride **2** and Ru-dimer **1**, respectively.

## Acknowledgements

Financial support from the Swedish Research Council and the Berzelius Center EXSELENT is gratefully acknowledged. We thank Johnson & Matthey (New Jersey, USA) for providing us with $[Ru_3(CO)_{12}]$.

[1] a) J. S. M. Samec, J. E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237–248; b) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226–236; c) P. G. Andersson, I. J. Munslow, "Modern Reduction Methods", Wiley-VCH, **2008**.

[2] a) S. Hashiguchi, A. Fujii, J. Takehera, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563; b) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102; c) D. A. Alonso, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588.

[3] a) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917; b) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061; c) J. Mao, D. C. Baker, *Org. Lett.* **1999**, *1*, 841–843.

[4] a) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503; b) V. Rautenstrauch, X. Hoang-Cong, R. Churlaud, K. Abdur-Rashid, R. H. Morris, *Chem. Eur. J.* **2003**, *9*, 4954–4967, and references therein.

[5] O. Pàmies, J. E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052–5058.

[6] a) Y. Shvo, D. Czarkie, Y. Rahamim, D. F. Chodosh, *J. Am. Chem. Soc.* **1986**, *108*, 7400–7402; b) N. Menashe, Y. Shvo, *Organometallics* **1991**, *10*, 3885–3891.

[7] M. L. S. Almeida, M. Beller, G-Z. Wang, J. E. Bäckvall, *Chem. Eur. J.* **1996**, *2*, 1533–1536.

[8] a) B. A. Persson, A. L. E. Larsson, M. Le Ray, J. E. Bäckvall, *J. Am. Chem. Soc.* **1999**, *121*, 1645–1650; b) O. Pàmies, J. E. Bäckvall, *Chem. Rev.* **2003**, *103*, 3247–3262.

[9] C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi, M. Kavana, *J. Am. Chem. Soc.* **2001**, *123*, 1090–1100.

[10] J. B. Johnson, J. E. Bäckvall, *J. Org. Chem.* **2003**, *68*, 7681–7684.

[11] a) C. P. Casey, G. A. Bikzhanova, Q. Cui, I. A. Guzei, *J. Am. Chem. Soc.* **2005**, *127*, 14062–14071; b) C. P. Casey, T. B. Clark, I. A. Guzei, *J. Am. Chem. Soc.* **2007**, *129*, 11821–11827.

[12] J. S. M. Samec, A. H. Éll, J. B. Åberg, T. Privalov, L. Eriksson, J. E. Bäckvall, *J. Am. Chem. Soc.* **2006**, *128*, 14293–14305.

[13] C. P. Casey, J. B. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 1883–1894.

[14] J. S. M. Samec, "Ruthenium-Catalyzed Hydrogen Transfer Involving Amines and Imines: Mechanistic Studies and Synthetic Applications", Dissertation, Stockholm University, April 29, **2005**.

[15] C. P. Casey, G. A. Bikzhanova, J. E. Bäckvall, L. Johansson, J. Park, Y. H. Kim, *Organometallics* **2002**, *21*, 1955–1959.

[16] The initial amount of Ru-dimer **1** was estimated to ca. 5% and all values have been corrected by subtraction of this amount. The figure shows the corrected values for [**1**].

[17] Reduction of cyclohexanone by hydride **2** in $CD_2Cl_2$ at −20 °C, in the presence of *N*-cyclohexylbenzylamine, was monitored by $^1$H NMR. The ratio Shvo dimer **1**/amine complex was about 1.2–1.3 at 20–30% conversion and about 1–1.1 at 70% conversion. The ratio is decreasing because the concentration of the hydride is decreasing about twice as fast as the concentration of the amine (see Supporting Information for full details).

[18] The expected ratio has been calculated from the ratio between ketoamine **3** and amino alcohol **4** according to Equation (1). This ratio changes during the reaction and if there were no cage effect, that is, that they compete equally in coordination to Ru, the amount of each complex should be equal to the accumulated concentration of

the corresponding amine. The concentrations [**3**] and [**4**] could not be obtained directly by integration in the NMR spectrum due to overlapping peaks. Instead they were obtained indirectly by calculations (see Supporting Information for details). $\frac{[\mathbf{5}]}{[\mathbf{7}]} = \int_{t=0}^{t=x} \frac{[\mathbf{4}]}{[\mathbf{3}]} = \mathrm{d}t$ (1)

[19] A graph for reduction of ketoamine complex **7** by Ru hydride **2** is given in the Supporting Information.

[20] Since the rate of reduction of ketoamine **3** (d[**3**]/d$t$) and ketoamine complex **7** (d[**7**]/d$t$) is approximately the same, d[**3**]/d$t$ was determined in each point, which afforded d[**7**]/d$t$ (d[**7**]/d$t$ $\approx$ d[**3**]/d$t$). [**7**] was corrected by addition of this amount and [**5**] was corrected by subtraction of the difference between measured [**7**] and corrected [**7**] in each point. New actual and expected ratio **5**/**7** were then calculated (see Supporting Information for details).

[21] a) T. M. Letcher, B. C. Bricknell, *J. Chem. Eng. Data* **1996**, *41*, 166–169; b) H. Umeyama, K. Morokuma, *J. Am. Chem. Soc.* **1977**, *99*, 1316–1332; c) F. Vernon, *J. Chromatogr.* **1971**, *63*, 249–257.

Received: June 18, 2008
Published online: September 24, 2008