DOI: 10.1002/chem.200700507

Catalytic Transfer Hydrogenation with Terdentate CNN Ruthenium Complexes: The Influence of the Base

Walter Baratta,* Katia Siega, and Pierluigi Rigo[a]

Abstract: The catalytic activity of the terdentate complex [RuCl(CNN)-(dppb)] (**A**) [dppb = $Ph_2P(CH_2)_4PPh_2$; *H*CNN = 6-(4′-methylphenyl)-2-pyridylmethylamine] in the transfer hydrogenation of acetophenone (**S**) with 2-propanol has been found to be dependent on the base concentration. The limit rate has been observed when NaO*i*Pr is used in high excess (**A**/base molar ratio > 10). The amino-isopropoxide species [Ru(O*i*Pr)(CNN)(dppb)] (**B**), which forms by reaction of **A** with sodium isopropoxide via displacement of the chloride, is catalytically active. The rate of conversion of acetophenone obeys second-order kinetics $v = k[\mathbf{S}][\mathbf{B}]$ with the rate constants in the range 218 ± 8 (40 °C) to $3000 \pm 70\ M^{-1}s^{-1}$ (80 °C). The activation parameters, evaluated from the Eyring equation are $\Delta H^{\neq} = 14.0 \pm 0.2$ kcal mol^{-1} and $\Delta S^{\neq} = -3.2 \pm 0.5$ eu. In a pre-equilibrium reaction with 2-propanol complex **B** gives the cationic species [Ru(CNN)(dppb)(HO*i*Pr)]$^+$ [O*i*Pr]$^-$ (**C**) with $K \approx 2 \times 10^{-5}$ M. The hydride species [RuH(CNN)(dppb)] (**H**), which forms from **B** via β-hydrogen elimination process, catalyzes the reduction of **S** and, importantly, its activity increases by addition of base. The catalytic behavior of the hydride **H** has been compared to that of the system **A**/NaO*i*Pr (1:1 molar ratio) and indicates that the two systems are equivalent.

Keywords: alkoxides · asymmetric catalysis · hydrides · ruthenium · transfer hydrogenation

Introduction

The reduction of polarized unsaturated compounds via transfer hydrogenation is a topic that has been extensively investigated in the last decade. A large number of transition-metal complexes have been found to catalyze the reduction of ketones and imines using 2-propanol or formic acid as hydrogen donor.[1] Among the different metal complexes, important results have been obtained with rhodium and ruthenium based catalysts. A significant breakthrough came in the early 90s with the discovery by Chowdhury and Bäckvall that the catalytic activity of $[RuCl_2(PPh_3)_3]$ could be increased by addition of a strong base (NaOH) to 2-propanol.[2] Further experiments showed that under basic conditions the dihydride derivative $[RuH_2(PPh_3)_4]$ is formed through the alkoxide route (i.e., via a β-hydrogen elimination reaction)[3] and this species has been found catalytically active.[4] For this system and other transition-metal complexes a stepwise mechanism has been suggested[5] that implies insertion of the incoming ketone into the metal–hydride bond with subsequent formation of metal alkoxide species.[6] This mechanism clearly differs from that of the direct hydrogen transfer proposed for the Meerwein–Ponndorf–Verley reaction with aluminum and other main group elements, in which the ketone interacts with the metal alkoxide.[7] A fundamental contribution to the development of new enantioselective transfer hydrogenation catalysts has been given by Noyori and co-workers in the late 90s, who observed that the activity of ruthenium arene complexes can be enhanced using N–O and N–N bidentate ligands where one N is a primary amine.[8] Evidence has been provided that during catalysis the *cis*-RuH/-NH_2 motif plays a fundamental role for the high activity. As a matter of fact, the ruthenium hydride amine species easily reacts with the ketone, affording the alcohol and a 16-electron ruthenium arene amide species. This process has been suggested to occur through an outer sphere mechanism with a concerted delivery of a N-H proton and a Ru-H hydride, and has been supported by quantum chemical methods in the gas phase.[9a–c] More recently, realistic modeling of the transfer hydrogenation in solution with ruthenium arene amine species leads to a concerted solvent-mediated mechanism with the substrate appearing as alkoxide-like intermediate.[9d] Impor-

[a] Prof. W. Baratta, Dr. K. Siega, Prof. P. Rigo
Dipartimento di Scienze e Tecnologie Chimiche
Università di Udine, Via Cotonificio 108
33100 Udine (Italy)
Fax: (+39) 0432-558-803
E-mail: inorg@dstc.uniud.it

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim WILEY InterScience DISCOVER SOMETHING GREAT

tantly, the Noyori system and the Shvo catalyst containing a RuH/-OH moiety,[10] which are regarded as bifunctional catalysts, do not require the presence of added base for the transfer hydrogenation. Kinetic studies based on deuterium isotope effect, performed by Casey[11] and Bäckvall[12] on the Noyori and Shvo catalysts, respectively, suggest that the hydrogen transfer from the alcohol to the ruthenium 16-electron species occurs through a concerted mechanism in both cases (i.e., simultaneous transfer of the C-H and O-H hydrogens from the alcohol). For the Noyori catalyst an outer sphere mechanism has been proposed, whereas for the Shvo system an inner sphere mechanism via initial coordination of the alcohol to the metal center and ring slippage has been suggested. No alcohol adducts have been isolated for these systems. However, these species should be considered very labile and therefore the inner and outer sphere mechanisms cannot be easily distinguished. The bifunctional catalysis works extremely well also in the hydrogenation of ketones using $RuCl_2$(diphosphine)(diamine) pre-catalysts.[13] Studies performed by Morris showed that the base is necessary for obtaining *cis*-RuH/-NH_2 species which are involved in the catalytic cycle.[14] Interestingly, high activity in hydrogenation is obtained with base/Ru ratio higher than 2, suggesting that fast catalytic reaction occurs in a certain range of effective pH values.[15]

Recently, we have reported that ruthenium complexes containing 2-(aminomethyl)pyridine (ampy) in association with phosphine or carbene ligands are extremely active catalysts for transfer hydrogenation.[16] Fast enantioselective reduction of ketones has been achieved with the system $RuCl_2$(diphosphine)(ampy) when chiral diphosphines are employed.[16d] With the related ligand 6-(4′-methylphenyl)-2-pyridylmethylamine the new terdentate complex of formula [RuCl(CNN)(dppb)] (**A**) (dppb = $Ph_2P(CH_2)_4PPh_2$) has been prepared which, in presence of base, displays extremely high activity for the transfer hydrogenation of ketones, affording TOF numbers up to $2.5\times10^6\ h^{-1}$ (Figure 1).[17]

It is worth noting that the hydride species [RuH(CNN)(dppb)] **H** reacts with ketones to give the corresponding alkoxide–amino complexes[17] and not the amide, revealing a rare example of reversible insertion[18] of ketones into the Ru–H bond.[19] Since, we have observed that the catalytic activity of the chloride complex **A** in 2-propanol is strongly affected by the base/Ru ratio, we decided to investigated the base influence on the catalytic transfer hydrogenation of acetophenone. These results provide evidence that the species displaying the alkoxide–amino motif RuOR/-NH_2,[14,17,20] in addition to the hydride-amino one RuH/-NH_2, are of fundamental importance for the fast transfer hydrogenation (Figure 1). The dependence of the base can be explained in terms of a pre-equilibrium involving the protonation of the ruthenium alkoxide leading to a cationic alcohol adduct.

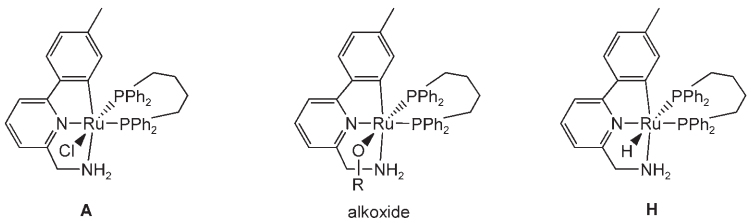
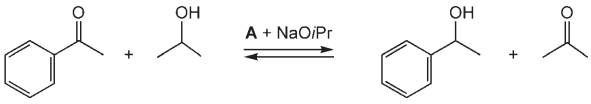


Figure 1. Terdentate CNN ruthenium complexes.

Results and Discussion

Influence of the concentration of the ruthenium complex A and the base on the transfer hydrogenation: The reduction of acetophenone, taken as model ketone, was carried out in 2-propanol using the CNN terdentate ruthenium complex **A** in presence of sodium isopropoxide, according to the [Eq. (1)].

All experiments have been performed using a 0.1 M solution of ketone in 2-propanol in order to achieve complete conversion into alcohol (1-phenylethanol ≥98% at the equilibrium)[1i] and the reaction was studied in the range between 40 °C and the refluxing temperature of 2-propanol. Typically, to a solution containing the substrate and the base NaO*i*Pr, the catalyst **A** was added and this represents the starting point of the reaction. It should be noted that without base no significant reduction of ketone was observed.



(1)

Using the pre-catalyst **A** at initial concentrations ranging from 0.01 to 0.1 mM (0.01–0.1 mol%) in presence of NaO*i*Pr, the conversion of acetophenone (**S**) in 1-phenylethanol, determined via GC, follows pseudo-first-order kinetics to over 95% conversion on the ketone concentration [Eq. (2)].

$$-\frac{d[S]}{dt} = k'[S] \qquad (2)$$

In order to establish the dependence of k' on the pre-catalyst **A** and the NaO*i*Pr base, we have carried out experiments at different concentrations of these species. First, as shown in Table 1, with an equimolar amount of **A** and NaO*i*Pr ($c_{\mathbf{A}} = c_b$ between 0.02 to 0.1 mM) at 60 °C the values of the apparent constant k' are in the range from 0.008 to 0.062 s^{-1} and show a nonlinear behavior of k' with respect to $c_{\mathbf{A}}$.

Second, when the concentration of $c_{\mathbf{A}}$ is kept at 0.01 mM, the increase of the amount of the base leads to a progressively faster reduction of acetophenone reaching a limit value (Figure 2). Thus, the k' constant is 0.021 s^{-1} when c_b is 0.02 mM and achieves the value of 0.050 s^{-1} when the c_b is 1.01 mM (Table 1).

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1. Rate constants k' for the conversion of acetophenone (0.1 M) to 1-phenylethanol with the complex **A** and NaO*i*Pr in 2-propanol.

$c_{\mathbf{A}}$ [M] $\times 10^3$	c_b [M] $\times 10^3$	k' [s^{-1}] $\times 10^3$
0.02[a]	0.02	8
0.05[a]	0.05	24
0.1[a]	0.10	62
0.01[b]	0.02	21
0.01[b]	0.03	32
0.01[b]	0.04	36
0.01[b]	0.06	38
0.01[b]	0.11	44
0.01[b]	0.21	47
0.01[b]	1.01	50

[a] Experiment carried out at 60 °C; [b] at reflux.

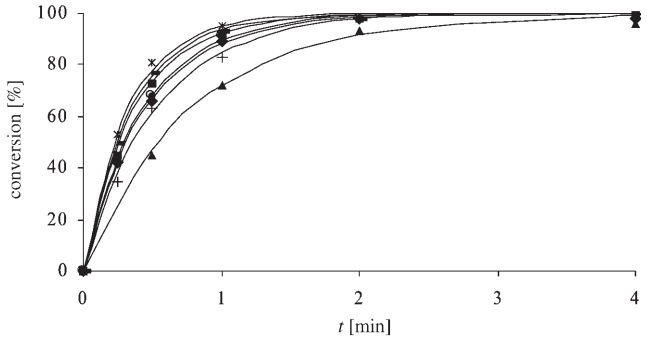


Figure 2. Conversion of acetophenone (0.1 M) with **A** ($c_{\mathbf{A}}$ = 0.01 mM) and NaO*i*Pr (c_b) at reflux: $c_b/c_{\mathbf{A}}$ = 2 (▲), 3 (+), 4 (◆), 6 (●), 11 (■), 21 (▪), 101 (*).

Third, by varying the pre-catalyst **A** (0.005 to 0.02 mM) at high base concentration (c_b = 2.00 mM), the apparent k' at 70 °C depends somehow linearly on $c_{\mathbf{A}}$ [Eq. (3)], as shown in Table 2.

$$k' \sim k c_{\mathbf{A}} \qquad (3)$$

Therefore, with a strong base excess the reduction of acetophenone follows a second-order rate, being first order respect to the catalyst [Eq. (4)].

$$-\frac{d[S]}{dt} \sim k c_{\mathbf{A}}[S] \qquad (4)$$

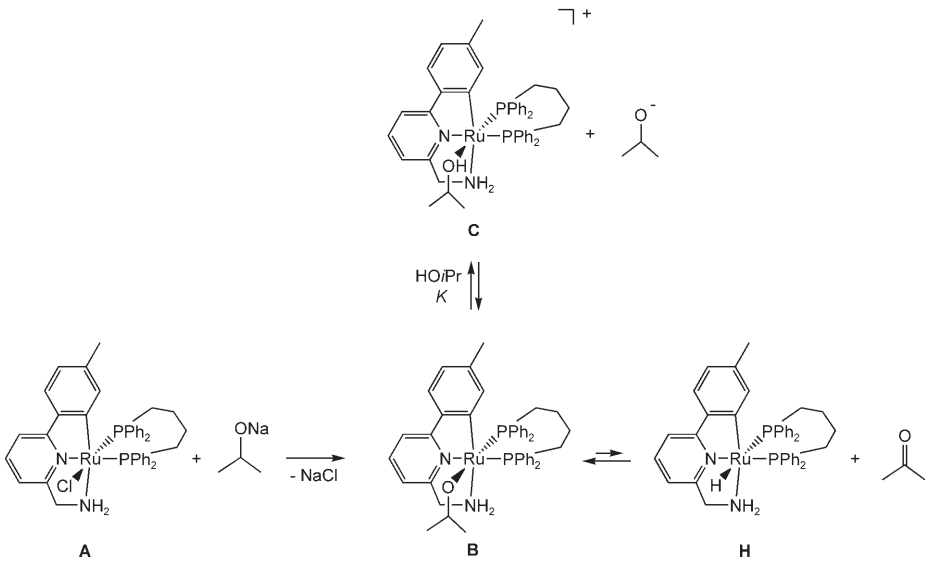
The higher activity obtained by increasing the base c_b at a fixed $c_{\mathbf{A}}$ (Figure 2) indicates that Equation (4) is correct only at high base concentration, suggesting the presence of a pre-equilibrium involving the catalytically active ruthenium species, which forms with sodium isopropoxide.

Table 2. Rate constants k' for the conversion of acetophenone (0.1 M) to 1-phenylethanol with the complex **A** and NaO*i*Pr (c_b = 2.00 mM) in 2-propanol at 70 °C.

$c_{\mathbf{A}}$ [M] $\times 10^3$	k' [s^{-1}] $\times 10^3$	$k'/c_{\mathbf{A}}$ [M^{-1} s^{-1}] $\times 10^{-3}$
0.005	8.0	1.60
0.0055	8.4	1.53
0.0066	12.5	1.89
0.0083	14.0	1.69
0.010	18.3	1.83
0.0125	20.0	1.60
0.020	35.0	1.75

In a previous study on stoichiometric reactions involving complex **A**, we have reported that reaction of **A** with NaO*i*Pr in a 2-propanol/toluene solution leads to the corresponding hydride **H** by elimination of acetone on evaporation of the medium.[17] The NMR analysis of the solution reveals that the first product is the alkoxide **B** obtained by substitution of the chloride with the isopropoxide through elimination of NaCl. This species, which is the main product in 2-propanol solution, affords reversibly the hydride **H** at temperature higher than 40 °C, according to the equilibrium shown in the Scheme 1.

When a ketone is added, no hydride is observed by NMR investigations, the reaction being shifted to the alkoxide. To note that the ruthenium alkoxide–primary amine complex [Ru(OCHPh$_2$)(CNN)(dppb)] has been isolated,[17] indicating that in this system the NH_2 group is not enough acidic to be deprotonated by the alkoxide ligand, by contrast to the ruthenium arene species that lead to ruthenium amide complexes.[8b] The catalytic transfer hydrogenation induced by **A** in basic conditions can be explained assuming that the key species is the alkoxide **B** which is promptly formed from **A** and NaO*i*Pr in 2-propanol. As a matter of fact, the rate is not significantly affected in the range of temperatures and base concentrations of this work when the reduction of ace-



Scheme 1. Formation of **B** and equilibrium reactions involving the alkoxide **B**.

© 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

tophenone is carried out with the preformed ruthenium alkoxide **B**, prepared from **2** and NaO*i*Pr in 2-propanol at 80 °C (10 min). The dependence of the rate on the base can be explained assuming that the complex **B** is involved in a rapid first step equilibrium with 2-propanol (i.e., protonation reaction), leading to the labile cationic alcohol complex **C**, according to the equilibrium constant K (Scheme 1). Importantly, control experiments show that reaction of **A** with Na[BAr^f_4] {Ar^f=3,5-$C_6H_3(CF_3)_2$} leads to the formation of the labile cationic alcohol adduct [Ru(CNN)(dppb)(HO*i*Pr)][BAr^f_4] {^{31}P NMR δ=58.4 and 42.2 ppm, ^2J(PP)=32 Hz, in 2-propanol with C_6D_6 (10% in volume) as inside lock}, which promptly reacts with one equivalent of Na*i*OPr in 2-propanol affording alkoxide **B**. The presence of a transition metal alkoxide versus alcohol adduct pre-equilibrium has previously been reported in transfer hydrogenation mediated by a rhodium(I) system,[21] whereas evidence for the formation of the cationic alcohol complex [RuH(diphosphine)(diamine)(ROH)]$^+$[(RO)(ROH)$_n$]$^-$, involved in the catalytic hydrogenation of ketones, has been provided in solution.[22] Furthermore, ruthenium complexes containing 2-propanol as ligand have also been characterized in the solid state.[23] The results of our experiments show that the rate of the catalytic reduction of acetophenone with 2-propanol in large excess follows second-order kinetics [Eq. (5)],

$$-\frac{d[S]}{dt} = k[B][S] \quad (5)$$

with the apparent kinetic constant k' reported in Equation (6).

$$k' = k[B] \quad (6)$$

From the pre-equilibrium reaction the concentration of **B** can be calculated from the initial values c_A and c_b, according to the constant K [Eq. (7)], assuming that the concentration of the hydride **H** is negligible because of the large excess of the ketone substrate.

$$K = \frac{[C][OiPr^-]}{[B]} = \frac{(c_A-[B])(c_b-[B])}{[B]} \quad (7)$$

In Equation (8) is reported the physically acceptable solution for the concentration of **B**.

$$[B] = \frac{c_A + c_b + K - \sqrt{(c_A + c_b + K)^2 - 4c_A c_b}}{2} \quad (8)$$

Combining Equations (6) and (8) leads to Equation (9) which correlates c_A, c_b and the apparent constants k' with the k and K ones.

$$\frac{k'}{c_A} = k\frac{c_A + c_b + K - \sqrt{(c_A + c_b + K)^2 - 4c_A c_b}}{2c_A} \quad (9)$$

When c_b=0 the ratio k'/c_A is zero, namely the pre-catalyst **A** is not active in absence of base, whereas for high values of c_b the ratio tends to k. By matching the experimental data with the computed trial curves, this equation allows to determine the k and K constants. In Figure 3 are reported

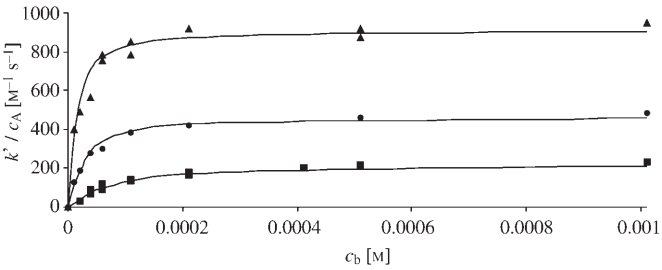


Figure 3. Experimental conditions: (■) c_A=0.05 mM, T=40 °C; (●) c_A=0.02 mM, T=50 °C; (▲) c_A=0.01 mM, T=60 °C.

the observed values of k'/c_A obtained from the conversion of acetophenone in the range from 40 to 60 °C versus the concentration of base c_b (c_A=0.01–0.05 mM).

Thus, at 40 °C the values for the kinetic and equilibrium constants are k=217±8 $M^{-1}s^{-1}$ and K=4.4±0.6×10^{-5} M, as reported in Table 3.

Table 3. Rate constants k and K for the conversion of acetophenone (0.1 M) to 1-phenylethanol with complex **A**.

T [K]	c_A [M]×10^3	**S**/c_A	k [$M^{-1}s^{-1}$]	K [M]×10^5
313	0.05	2000	217±8	4.4±0.6
323	0.02	5000	460±10	1.8±0.2
333	0.01	10000	910±20	0.9±0.1
333	0.05	2000	790±30	2.6±0.4
343	0.01	10000	1760±30	1.0±0.1
353	0.01	10000	3000±70	2.3±0.2
reflux	0.01	10000	4720±90	1.6±0.1

Experiments carried out at 70, 80 °C and at refluxing temperature of 2-propanol with c_A=0.01 mM lead to the data reported in Figure 4, which allow to determine the k and K constants at different temperatures.

The k values are in the range 217±8 $M^{-1}s^{-1}$ at 40 °C to 4720±90 $M^{-1}s^{-1}$ at refluxing conditions (Table 3). To check

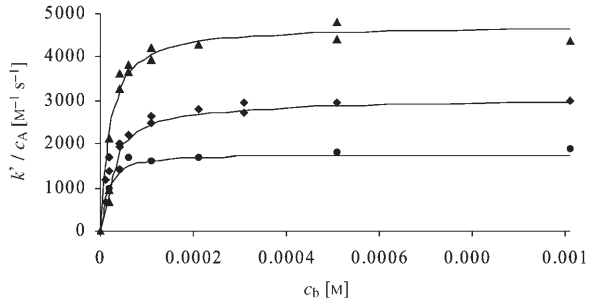


Figure 4. Experimental conditions: c_A=0.01 mM, (●) T=70 °C, (◆) T=80 °C, (▲) reflux.

© 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

the model at different ruthenium concentrations, a set of experiments was carried out at $c_A = 0.05$ mM at 60 °C, leading to $k = 790 \pm 30\ M^{-1}\ s^{-1}$, to be compared with $910 \pm 20\ M^{-1}\ s^{-1}$ for $c_A = 0.01$ mM. Using the Eyring equation and performing a global fitting of the conversion values from 40 to 80 °C provides the activation parameters $\Delta H^{\neq} = 14.0 \pm 0.2$ kcal mol^{-1}, $\Delta S^{\neq} = -3.2 \pm 0.5$ eu, and $\Delta G^{\neq}_{298} = 15.0 \pm 0.2$ kcal mol^{-1}. The Eyring plot of $\ln(k/T)$ versus $1/T$ in the range from 313 to 353 K is reasonably linear (Figure 5), indicating that the catalytic system does not undergo deactivation in this range of temperatures.

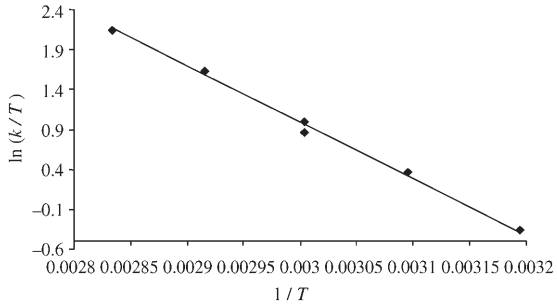


Figure 5. Eyring plot of the rate constants for the catalytic transfer hydrogenation with **A**.

The value for the enthalpy of activation is lower compared with that obtained for the BINOLate/aluminum/2-propanol/acetophenone system involving a direct hydrogen transfer ($\Delta H^{\neq} = 18.5$ kcal mol^{-1}, $\Delta S^{\neq} = -11.7$ eu, $\Delta G^{\neq}_{298} = 21.8$ kcal mol^{-1}).[24] The value of $\Delta S^{\neq}$ is consistent with a transition state with substantial zero variation of the entropy of activation, suggesting that no substantial rearrangement occurs in the rate determining step. This could be in agreement with an intramolecular conversion of RuOR into RuH/ketone in the alcohol media, via cleavage of the C–H bond and affording the ketone bound to the $RuNH_2$ moiety through hydrogen bonds[25] and involving 2-propanol (see later discussion on the catalytic cycle).

The determination of the equilibrium constants through the curvature of the best fitting does not allow to obtain K values with great accuracy (Table 3), nevertheless these results indicate that the alkoxide **B** can be regarded as a weak base (K mean value $= 2 \times 10^{-5}$ M) which in neat 2-propanol is partially protonated, leading to the cationic alcohol complex **C**. According to this model the alkoxide **B** is prone to induce the hydrogen transfer, whereas **C** should be considered not active and consequently addition of a strong base is required to achieve high catalytic activity. This effect is evident when the experiments are carried out at low ruthenium loading for which a high base/Ru molar ratio is necessary to achieve the best performance and suggesting that the catalytic process works well above a certain effective pH value. The obtained values of k and K allow to calculate the apparent constants k' at different catalyst and base concentrations, the data reported in Tables 1 and 2 being entirely consistent.

Transition metal hydride complexes have been proven to be key intermediates involved in manifold catalytic processes.[26] Importantly, the monohydride derivative **H** has been found to catalyze the transfer hydrogenation of acetophenone without base, and this result can be compared with those obtained with mono-[8b] and dihydride ruthenium complexes which have been found to be catalytically active.[2,27] Surprisingly, when a base is added to **H** the rate of conversion increases significantly, in contrast to the well-known arene-*N*-tosylethylenediamine ruthenium systems, which are not affected.[8b] Thus, addition of several equivalents of NaO*i*Pr to the hydride **H** leads to a considerable increase of rate of conversion (Figure 6).

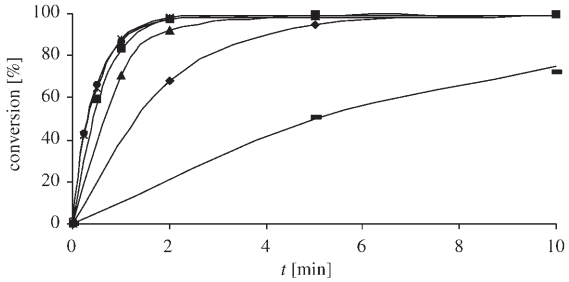


Figure 6. Conversion of acetophenone (0.1 M) with **H** ($c_H = 0.01$ mM) and NaO*i*Pr (c_b) at reflux: $c_b/c_H = 0$ (■), 1 (◆), 3 (▲), 5 (■), 10 (●), 100 (*).

By increasing the concentration of complex **H**, reduction of acetophenone occurs in a shorter time, as shown in Figure 7. It is to point out that when the chloride **A** is employed with one molar amount of NaO*i*Pr, this system displays a slightly faster rate respect to the hydride **H** (Figure 7).

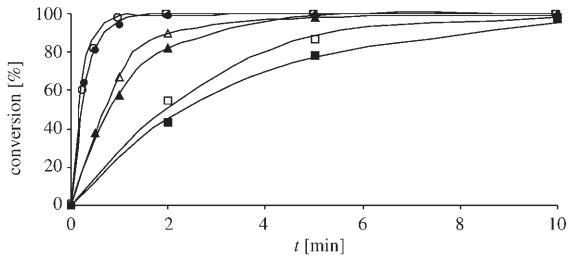


Figure 7. Conversion of acetophenone (0.1 M) with **H** ($c_H = 0.02$ (■), 0.05 (▲), 0.1 (●) mM) and with the system **A**/NaO*i*Pr (1:1 molar ratio) ($c_A = c_b = 0.02$ (□), 0.05 (△), 0.1 (○) mM) at reflux.

Since the latter complex is involved in the catalytic cycle, its lower activity may be tentatively ascribed to the high sensitivity of **H** toward dioxygen and moisture. Interestingly, in the catalytic racemization of (*S*)-1-phenylethanol that occurs within the coordination sphere of pentaphenylcyclopentadienyl ruthenium complexes, the hydride derivative is significantly less active than the corresponding alkoxide, as recently reported by Bäckvall and co-workers, who suggest

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

that the hydride is not an abundant species in the catalytic process.[28] Modifying Equation (9) for the hydride gives Equation (10), in which k' depends on the initial concentration of **H** ($c_{\mathbf{H}}$) and the base.

$$\frac{k\prime}{c_{\mathrm{H}}} = k\frac{2c_{\mathrm{H}} + c_{\mathrm{b}} + K - \sqrt{(2c_{\mathrm{H}} + c_{\mathrm{b}} + K)^2 - 4c_{\mathrm{H}}(c_{\mathrm{b}} + c_{\mathrm{H}})}}{2c_{\mathrm{H}}} \qquad (10)$$

The values of $k'/c_{\mathbf{H}}$ as function of c_{b} are reported in Figure 8.

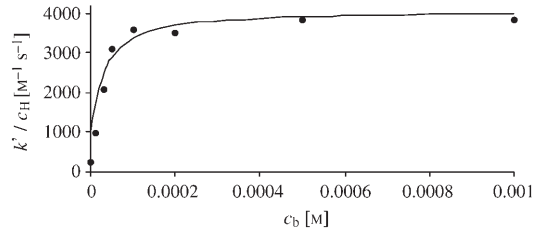


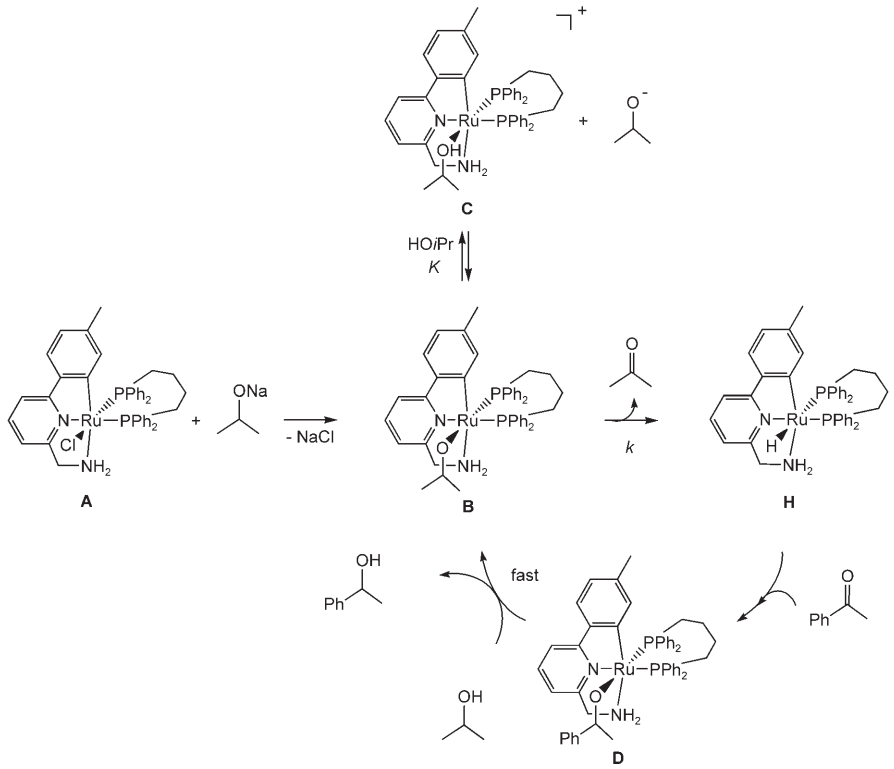
Figure 8. Experimental conditions: $c_{\mathbf{H}} = 1.0 \times 10^{-5}$ M at reflux.

For $c_{\mathrm{b}} = 0$ the ratio $k'/c_{\mathbf{H}}$ is different from zero and this agrees with the catalytic activity of the hydride **H** without base, whereas for high values of c_{b} the ratio tends to k. By matching the experimental data at reflux with the computed trial curves, this equation allows to determine $k = 4100\,\mathrm{M^{-1}\,s^{-1}}$ and $K = 2.2 \times 10^{-5}$ M, which are values relatively close to those obtained starting from the chloride **A**. Thus, these results show that under catalytic conditions the hydride **H** converts quickly to the alkoxide species **B** whose activity, as previously described, depends on the added base because of the pre-equilibrium involving **C**. The similar results obtained for **H** and the **A**/Na*i*OPr (1:1 molar ratio) system indicate that formation of **B** is fast in both cases, compared with the rate of the overall catalytic reaction. Therefore, this study shows that the base is necessary not only to generate the catalytically active hydride species, but it has a strong effect after the hydride has been formed, an observation that was not previously reported.

In Scheme 2 is displayed the proposed catalytic cycle which accounts for the influence of the base through a pre-equilibrium reaction involving the ruthenium isopropoxide.

The pre-catalyst **A** reacts with sodium isopropoxide leading to the specie **B** that rapidly equilibrates with the cationic alcohol adduct **C** (catalyst reservoir). Complex **B** undergoes a β-hydrogen elimination process affording the ruthenium hydride **H** which subsequently reacts with acetophenone leading to the ruthenium alkoxide **D**. In the final step of the catalytic cycle the ruthenium alkoxide reacts fast with 2-propanol, which is in large excess, affording 1-phenylethanol and the isopropoxide **B** that closes the cycle. The formation of **H** from **B** is likely to be rate determining step of the catalytic transfer hydrogenation in which most of ruthenium is present as **B** and **C** species, according to the base concentration. Experiments carried out with [D_8]-2-propanol allowed to determine the apparent constant k'_{D}. A comparison of the data obtained at 40 and 60 °C gives $k_{\mathrm{CHOH}}/k_{\mathrm{CDOD}} = 7.2$ and 7.9, respectively, which are high values consistent with a rate controlling step involving a C–H bond cleavage. It is worth pointing out that, while this mechanism that involves ruthenium alkoxides and the hydride is better referred as inner sphere, the overall process is mediated by hydrogen bonds with the NH_2 group. As a matter of fact, the amino protons can interact with the ketone facilitating the insertion of the carbonyl compound into the Ru–H bond of **H**, as well as the reverse β-hydrogen elimination reaction from **B** through interaction of the NH with the oxygen of the alkoxide,[17] weakening the Ru–OR bond and affording the C–H activation (Figure 9).

Theoretical calculations in the gas phase indicate that the ruthenium alkoxide–amine complexes are the most stable



Scheme 2. Proposed catalytic cycle for the transfer hydrogenation of acetophenone with **A**.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

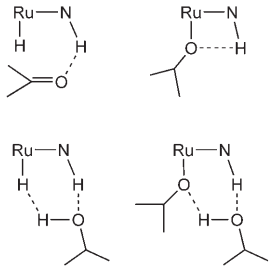


Figure 9. Hydrogen bonds involving the amino group in **H** and **B**.

species along the reactions pathway and are stabilized through an intramolecular O···HN hydrogen bond.[9b,29] This mechanism of the β-hydrogen elimination could be related to that proposed by Milstein for the β-hydrogen elimination of *trans*-[HIr(OCH_3)(C_6H_5)-(PMe_3)$_3$] which occurs in methanol without requiring a vacant *cis* coordination site and via hydrogen-bonding network with the alcohol.[30] Alternatively, the formation of **H** from the alkoxide **B** could follow the classical β-hydrogen elimination route, with an empty site originated through decoordination of the *cis* NH_2 function. As a matter of fact, the NMe_2 analogous complex **A** exhibits a fluxional behavior with the NMe_2 that undergoes easy decoordination from the ruthenium metal center.[17b] It should be noted that, we have found no evidence in 2-propanol of the formation of the ruthenium amide, that is, the species which would originate from **B** via 2-propanol elimination.

In the reaction media both **H** and **B** should be involved in hydrogen bonding, namely the amino protons can interact with 2-propanol, leading to the corresponding alcohol adducts stabilized via two hydrogen bonds and affording six-membered cycles (Figure 9). As a matter of fact, the interaction between the alkoxide [Ru($OCHPh_2$)(CNN)(dppb)] and $HOCHPh_2$, leading to the corresponding metal alkoxide–alcohol adduct,[31] has previously been established via NMR in [D_6]-benzene.[17] Therefore, the NH_2 group plays a fundamental role in favoring the association and exchange processes involving ketones and alcohols, thus accelerating the entire catalytic reaction by means of hydrogen bonds, a well-known cooperative effect of enzymes.[32] The interaction of the catalytically active species with alcohol, which cannot be regarded as innocent solvent, may lead to a mechanism different from that proposed (metal–ligand bifunctional mechanism) and supported by calculations in the gas phase, as recently suggested by Handgraaf and Meijer.[9d] This could be relevant also for the enantioselectivity of the hydrogen transfer when chiral ruthenium catalysts are employed.[33] To note that in the hydrogenation of carbonyl compounds with NH_2 or OH bifunctional ruthenium catalytic systems, the alcohols, used as solvents, play an important role, increasing the activity[15a,34] and also affecting the enantioselectivity.[35]

As regards the substitution in M–OR complexes of the type **B**, a high exchange rate of the alkoxide ligand with alcohol has been observed through NMR experiments,[17] in agreement with the properties of these species.[6a,36] According to the studies of Bergman, this can be reasonably ascribed to the hydrogen-bond interactions between the alkoxide and the alcohol. Although one could expect an increase of the alkoxide exchange at higher NaO*i*Pr concentration in 2-propanol, the fast alkoxide substitution is mediated by alcohols and is not reasonably rate determining step. Interestingly, the high reactivity of the alkoxides of the type **B** in the β-hydrogen transfer reactions seems to be primarily due to the formation of hydrogen bond network. The concomitant presence of a *cis* NH_2 group to the OR ligand in addition to a *trans* phosphorus atom[37] may weaken the Ru–OR bond, allowing rapid transformations.

Conclusion

The present work on terdentate ruthenium complexes of formula [RuX(CNN)(dppb)] (X = Cl, H, OR) shows that the isopropoxide **B** and the hydride **H** are catalytically active species. In 2-propanol a pre-equilibrium involving **B** and the cationic alcohol complex **C** is suggested on the basis of kinetic results which show that the activity of the ruthenium system increases at higher base concentration. Complex **B** leads to the hydride **H** via elimination of acetone, while subsequent insertion of acetophenone affords the ruthenium alkoxide **D**. The facile β-hydrogen elimination in **B** is likely to occur via hydrogen bonds between the RuOR moiety and the amino group. Hydrogen bonds between RuOR and HOR are also responsible of the fast displacement of the alkoxide ligands and in particular the formation of **B** from **D**. Therefore, this hydrogen transfer process that entails ruthenium alkoxides and the hydride is better referred as an inner sphere mechanism. The results obtained from the ruthenium chloride **A** are related to those obtained with the hydride **H** which rapidly converts to **B** and consequently the activity of the hydride is affected by the base concentration, an observation that was not previously reported. Further investigations on the reaction mechanism and kinetics are in progress to gain more details of the catalytic cycle.

Experimental Section

Typical procedure for the catalytic hydrogen transfer reaction: Complex **A** (2.0 mg, 2.6 μmol) was dissolved in freshly distilled 2-propanol (5 mL). Acetophenone (2 mmol) was dissolved in 2-propanol (19 mL) with the appropriate amount of NaO*i*Pr (0.1 M solution in 2-propanol) and the solution was heated under argon. By addition of the proper volume of the solution containing **A** the reduction of the ketone starts immediately and the yield was determined by GC.

Kinetic analysis: A global fitting was used for calculating the k, K constants and the activation parameters ($\Delta H^{\neq}$, $\Delta S^{\neq}$) using the Eyring equation $k=(k_B/h)T\exp(-\Delta H^{\neq}/RT)\exp(\Delta S^{\neq}/R)$, where k_B is Boltzmann's constant, h is Planck's constant and R is the ideal gas constant. Error analysis for k, $\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta G^{\neq}$ was performed with the SOLVERSTAT program.[38]

Acknowledgements

This work was supported by the Ministero dell'Università e della Ricerca (MUR). The authors thank Professor Jan Bäckvall (Stockholm University) and Dr. M. Bassetti (CNR, Roma) for helpful discussions and P. Polese (Udine University) for the error analysis.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[1] a) J. S. M. Samec, J. E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237; b) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226; c) S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201; d) K. Everaere, A. Mortreux, J. F. Carpentier, *Adv. Synth. Catal.* **2003**, *345*, 67; e) J. E. Bäckvall, *J. Organomet. Chem.* **2002**, *652*, 105; f) M. Wills, M. Palmer, A. Smith, J. Kenny, T. Walsgrove, *Molecules* **2000**, *5*, 4; g) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry* **1999**, *10*, 2045; h) S. Gladiali, G. Mestroni in *Transition Metals for Organic Synthesis, Vol. 2* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, p. 97; i) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97; j) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, *92*, 1051.

[2] R. L. Chowdhury, J. E. Bäckvall, *J. Chem. Soc. Chem. Commun.* **1991**, 1063.

[3] a) S. P. Nolan, T. R. Nelderrain, R. H. Grubbs, *Organometallics* **1997**, *16*, 5569; b) M. A. Esteruelas, E. Sola, L. A. Oro, H. Werner, U. Meyer, *J. Mol. Catal.* **1988**, *45*, 1; c) B. N. Chaudret, D. J. Cole-Hamilton, R. S. Nohr, G. Wilkinson, *J. Chem. Soc. Dalton Trans.* **1977**, 1546.

[4] A. Aranyos, G. Csjernyik, K. J. Szabó, J. E. Bäckvall, *Chem. Commun.* **1999**, 351.

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

[6] a) J. R. Fulton, A. W. Holland, D. J. Fox, R. G. Bergman, *Acc. Chem. Res.* **2002**, *35*, 44; b) H. E. Bryndza, W. Tam, *Chem. Rev.* **1988**, *88*, 1163.

[7] a) C. F. De Graauw, J. A. Peters, H. van Bekkum, J. Huskens, *Synthesis* **1994**, 1007; b) E. C. Ashby, *Acc. Chem. Res.* **1988**, *21*, 414.

[8] a) J. Takehara, S. Hashiguchi, A. Fujii, S. Inoue, T. Ikariya, R. Noyori, *Chem. Commun.* **1996**, 233; b) K. J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int.* **1997**, *109*, 297; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285.

[9] a) D. A. Alonso, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc.* **1999**, *121*, 9580; b) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466; c) D. G. I. Petra, J. N. H. Reek, J. W. Handgraaf, E. J. Meijer, P. Dierkes, P. C. J. Kamer, J. Brussee, H. E. Schoemaker, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2000**, *6*, 2818; d) J. W. Handgraaf, E. J. Meijer, *J. Am. Chem. Soc.* **2007**, *129*, 3099.

[10] a) Y. Shvo, D. Czarkie, Y. Rahamin, *J. Am. Chem. Soc.* **1986**, *108*, 7400; b) N. Menashe, Y. Shvo, *Organometallics* **1991**, *10*, 3885; c) N. Menashe, E. Salant, Y. Shvo, *J. Organomet. Chem.* **1996**, *514*, 97.

[11] C. P. Casey, J. B. Johnson, *J. Org. Chem.* **2003**, *68*, 1998.

[12] J. B. Johnson, J. E. Bäckvall, *J. Org. Chem.* **2003**, *68*, 7681.

[13] H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem.* **1998**, *110*, 1792; *Angew. Chem. Int. Ed.* **1998**, *37*, 1703.

[14] K. Abdur-Rashid, S. E. Clapham, A. Hadzovic, J. N. Harvey, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2002**, *124*, 15104.

[15] a) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490; b) R. J. Hamilton, S. H. Bergens, *J. Am. Chem. Soc.* **2006**, *128*, 13700.

[16] a) W. Baratta, P. Da Ros, A. Del Zotto, A. Sechi, E. Zangrando, P. Rigo, *Angew. Chem.* **2004**, *116*, 3668; *Angew. Chem. Int. Ed.* **2004**, *43*, 3584; b) W. Baratta, A. Del Zotto, G. Esposito, A. Sechi, M. Toniutti, E. Zangrando, P. Rigo, *Organometallics* **2004**, *23*, 6264; c) W. Baratta, J. Schütz, E. Herdtweck, W. A. Herrmann, P. Rigo, *J. Organomet. Chem.* **2005**, *690*, 5570; d) W. Baratta, E. Herdtweck, K. Siega, M. Toniutti, P. Rigo, *Organometallics* **2005**, *24*, 1660.

[17] a) W. Baratta, G. Chelucci, S. Gladiali, K. Siega, M. Toniutti, M. Zanette, E. Zangrando, P. Rigo, *Angew. Chem.* **2005**, *117*, 6370; *Angew. Chem. Int. Ed.* **2005**, *44*, 6214; b) W. Baratta, M. Bosco, G. Chelucci, A. Del Zotto, K. Siega, M. Toniutti, E. Zangrando, P. Rigo, *Organometallics* **2006**, *25*, 4611.

[18] a) D. M. Hoffman, D. Lappas, D. A. Wierda, *J. Am. Chem. Soc.* **1993**, *115*, 10538; b) M. A. Esteruelas, C. Valero, L. A. Oro, U. Meyer, H. Werner, *Inorg. Chem.* **1991**, *30*, 1159.

[19] a) C. J. A. Daley, S. H. Bergens, *J. Am. Chem. Soc.* **2002**, *124*, 3680; b) Y. Hayashi, S. Komiya, T. Yamamoto, A. Yamamoto, *Chem. Lett.* **1984**, 1363.

[20] T. Koike, T. Ikariya, *Organometallics* **2005**, *24*, 724.

[21] C. De Bellefon, N. Tanchoux, *Tetrahedron: Asymmetry* **1998**, *9*, 3677.

[22] C. A. Sandoval, Y. Yamaguchi, T. Ohkuma, K. Kato, R. Noyori, *Magn. Reson. Chem.* **2006**, *44*, 66.

[23] a) C. S. Yi, Z. He, I. A. Guzei, *Organometallics* **2001**, *20*, 3641; b) A. Currao, N. Feiken, A. Macchioni, R. Nesper, P. S. Pregosin, G. Trabesinger, *Helv. Chim. Acta* **1996**, *79*, 1587.

[24] R. Cohen, C. R. Graves, S. T. Nguyen, J. M. L. Martin, M. A. Ratner, *J. Am. Chem. Soc.* **2004**, *126*, 14796.

[25] a) T. Steiner, *Angew. Chem.* **2002**, *114*, 50; *Angew. Chem. Int. Ed.* **2002**, *41*, 48; b) G. A. Jeffrey in *An Introduction to Hydrogen Bonding*, Oxford University Press, Oxford, **1997**; c) G. R. Desiraju, T. Steiner in *The Weak Hydrogen Bond*, Oxford University Press, Oxford, **1999**; d) L. Brammer, *Dalton Trans.* **2003**, 3145; e) G. Aullón, D. Bellamy, L. Brammer, E. A. Bruton, A. G. Orpen, *Chem. Commun.* **1998**, 653.

[26] a) P. Espinet, A. C. Albéniz in *Fundamentals of Molecular Catalysis, Current Methods in Inorganic Chemistry, Vol. 3* (Eds.: H. Kurosawa, A. Yamamoto), Elsevier, Amsterdam, **2003**, Chapter 6, p. 293; b) H. Jacobsen, H. Berke in *Recent Advances in Hydride Chemistry* (Eds.: M. Peruzzini, R. Poli), Elsevier, Amsterdam, **2001**, Chapter 4, p. 89; c) N. Koga, K. Morokuma, *Chem. Rev.* **1991**, *91*, 823.

[27] V. Cadierno, P. Crochet, J. Díez, S. E. García-Garrido, J. Gimeno, *Organometallics* **2004**, *23*, 4836.

[28] B. Martín-Matute, M. Edin, K. Bogár, F. B. Kaynak, J. E. Bäckvall, *J. Am. Chem. Soc.* **2005**, *127*, 8817.

[29] J. W. Handgraaf, J. N. H. Reek, E. J. Meijer, *Organometallics* **2003**, *22*, 3150.

[30] O. Blum, D. Milstein, *J. Organomet. Chem.* **2000**, *593–594*, 479.

[31] a) Y. J. Kim, K. Osakada, A. Takenaka, A. Yamamoto, *J. Am. Chem. Soc.* **1990**, *112*, 1096; b) K. Osakada, K. Ohshiro, A. Yamamoto, *Organometallics* **1991**, *10*, 404; c) S. E. Kegley, C. J. Schaverien, J. H. Freudenberger, R. G. Bergman, S. P. Nolan, C. D. Hoff, *J. Am. Chem. Soc.* **1987**, *109*, 6563.

[32] a) D. B. Grotjahn, *Chem. Eur. J.* **2005**, *11*, 7146; b) T. E. Creighton in *Proteins: Structures and Molecular Properties*, W. H. Freeman, New York, **1993**, p. 418.

[33] P. Brandt, P. Roth, P. G. Andersson, *J. Org. Chem.* **2004**, *69*, 4885.

[34] a) M. Ito, M. Hirakawa, K. Murata, T. Ikarya, *Organometallics* **2001**, *20*, 379; b) C. P. Casey, J. B. Johnson, S. W. Singer, O. Cui, *J. Am. Chem. Soc.* **2005**, *127*, 3100.

[35] T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q. Lin, Y. Wei, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2005**, *127*, 8288.

[36] a) M. S. Sanford, L. M. Henling, M. W. Day, R. H. Grubbs, *Angew. Chem.* **2000**, *112*, 3593; *Angew. Chem. Int. Ed.* **2000**, *39*, 3451; b) Y. Guary, J. A. Ayllon, S. Sabo-Etienne, B. Chaudret, *Inorg. Chem.* **1998**, *37*, 640; c) P. L. Holland, R. A. Andersen, R. G. Bergman, J. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1997**, *119*, 12800; d) D. C. Bradley, R. C. Mehrotra, I. P. Rothwell, A. Singh in *Alkoxo and Aryloxo Derivatives of Metals*, Academic Press, New York, **2001**, Chapter 2.

[37] a) T. G. Appleton, H. C. Clark, L. E. Manzer, *Coord. Chem. Rev.* **1973**, *10*, 335; b) J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke in *Principles and Application of Organotransition Metal Chemistry*, University Science Books, Mill Valey, CA, **1987**; c) J. C. Toledo, B. S. Lima Neto, D. W. Franco, *Coord. Chem. Rev.* **2005**, *249*, 419.

[38] C. Comuzzi, P. Polese, A. Melchior, R. Portanova, M. Tolazzi, *Talanta* **2003**, *59*, 67.

Received: April 2, 2007
Published online: June 20, 2007

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim