Published in European Journal of Inorganic Chemistry 30, 4736 – 4742, 2007
which should be used for any reference to this work

Water-Soluble Phenanthroline Complexes of Rhodium, Iridium and Ruthenium for the Regeneration of NADH in the Enzymatic Reduction of Ketones

Jérôme Canivet,[a] Georg Süss-Fink,*[a] and Petr Štěpnička[b]

Keywords: Cationic complexes / Cofactor regeneration / Chemoenzymatic catalysis / Enantioselective catalysis / Transfer hydrogenation

The nicotinamide coenzyme NADH, consumed in enantioselective reduction of ketones catalysed by alcohol dehydrogenases, needs to be regenerated in order to maintain enzymatic activity. We therefore studied the catalytic potential of the cationic complexes $[(\eta^5\text{-}C_5Me_5)Rh(N\cap N)Cl]^+$ (**1**: N∩N = 1,10-phenanthroline; **2**: N∩N = 5-nitro-1,10-phenanthroline; **3**: N∩N = 5-amino-1,10-phenanthroline), $[(\eta^5\text{-}C_5Me_5)Ir(N\cap N)Cl]^+$ (**4**: N∩N = 5-nitro-1,10-phenanthroline) and $[(\eta^6\text{-}C_6Me_6)Ru(N\cap N)Cl]^+$ (**5**: N∩N = 5-nitro-1,10-phenanthroline), isolated as the water-soluble chloride salts, for transfer hydrogenation of NAD^+ to give NADH in aqueous solution. The best results were obtained with rhodium complex **1**, which gave catalytic turnover frequencies up to 2000 h^{-1} in aqueous solution at pH 7 and 60 °C with sodium formate as the hydrogen source. When this NADH-regenerating catalytic system is combined with NADH-dependent enzymes, it is possible to chemoenzymatically reduce prochiral ketones such as acetophenone or 4-phenylbutan-2-one with high enantioselectivity. Combination of horse liver alcohol dehydrogenase (HLADH) or alcohol dehydrogenase from *Rhodococcus sp.* (S-ADH) with **1**/formate as the NADH-regenerating system resulted in *ee* values up to 98%, depending on the nature of the substrate and the enzyme. In order to explain the different catalytic activities, the electrochemical behaviour of complexes **1**–**5** has been studied.

Introduction

There is an increasing demand for enantiopure biologically active compounds and their precursors.[1] The transition-metal-based enantioselective hydrogenation or transfer hydrogenation of ketones in organic solvents[2–10] as well as in aqueous solutions[11–21] is one of the most commonly used synthetic approaches. Biotransformations of organic substrates by various enzymes have also found widespread applications, particularly because of their capability to efficiently perform enantioselective transformations. The use of redox enzymes for synthetic purposes, however, has been limited by the need of cofactor regeneration.[22] Therefore, practical methods for the regeneration of coenzyme 1,4-NADH, the reduced form of nicotinamide adenine dinucleotide (NAD^+), are still of significant importance in the field of biocatalysis.

Conversion of NAD^+ to NADH by enzymatic,[23–26] photo- or electrochemical[27–29] methods has been extensively studied in order to increase the rate of cofactor regeneration while maintaining the necessary 1,4-dihydro regioselectivity. More than ten years ago Steckhan et al. introduced the dicationic (aqua)(bipyridine)rhodium complex $[(\eta^5\text{-}C_5Me_5)Rh(bipy)(OH_2)]^{2+}$ as a catalyst for the regeneration of NADH by using the formate anion as the hydrogen source in aqueous solution.[30,31] In a pioneering paper, Fishpp et al. extensively studied kinetic and mechanistic details of regioselective catalytic reduction by using a variety of 3-pyridinium NAD^+ models in the presence of $[(\eta^5\text{-}C_5Me_5)Rh(bipy)(OH_2)]^{2+}$.[32–35] This NADH-regenerating catalytic system was applied to the coupled chemoenzymatic enantioselective transfer hydrogenation of ketones in aqueous solution by combining NADH regeneration by an organorhodium complex and enantioselective ketone reduction performed by an alcohol dehydrogenase (ADH). Steckhan et al. described the transfer hydrogenation of 4-phenylbutan-2-one to the corresponding alcohol using ADH from horse liver with enantiomeric excesses up to 96%.[22] More recently, Schmid et al. reported a system based on ADH from *Thermus sp.* coupled with $[(\eta^5\text{-}C_5Me_5)Rh(bipy)(OH_2)]^{2+}$-promoted regeneration of NADH, which allowed the reduction of 3-methylcyclohexanone with an enantiomeric excess up to 97%.[1]

In this paper we report a series of water-soluble rhodium, iridium and ruthenium complexes containing 1,10-phenanthroline or its 5-substituted analogues as chelating *N*,*N*-donor ligands and the catalytic potential of these complexes for the regeneration of NADH in the chemoenzymatic re-

[a] Institut de Chimie, Université de Neuchâtel,
Case postale 158, 2009 Neuchâtel, Switzerland
E-mail: georg.suess-fink@unine.ch
[b] Department of Inorganic Chemistry, Faculty of Natural Science, Charles University in Prague
Hlavova 2030, 12840 Prague, Czech Republic

duction of ketones. The electrochemical behaviour of the complexes is also discussed.

Results and Discussion

Synthesis of Phenanthroline Complexes

Complexes $[(\eta^5\text{-}C_5Me_5)MCl_2]_2$ (M = Rh, Ir) react at room temperature in dichloromethane solution with 1,10-phenanthroline (phen) or with its 5-nitro or 5-amino derivatives to afford quantitatively the cationic complexes $[(\eta^5\text{-}C_5Me_5)M(N\cap N)Cl]^+$ (**1**: M = Rh, N∩N = phen; **2**: M = Rh, N∩N = 5-NO_2-phen; **3**: M = Rh, N∩N = 5-NH_2-phen; and **4**: M = Ir, N∩N = 5-NO_2-phen) [Equation (1)]. These cations are easily isolated as their chloride salts.

$$\tfrac{1}{2}[(\eta^5\text{-}C_5Me_5)MCl_2]_2 + N\cap N \rightarrow [(\eta^5\text{-}C_5Me_5)Rh(N\cap N)Cl]^+ + Cl^- \quad (1)$$

The chloride salts of **1**–**4** are yellow-orange solids that have a high solubility in water, a property that is used to remove unreacted starting material after the synthesis. As there is a risk of slow hydrolysis in water, the aqueous solutions are immediately filtered, and the filtrates are concentrated to dryness to give the analytically pure salts [**1**–**4**]Cl. All compounds have been characterised by ^1H and ^{13}C NMR spectroscopy, mass spectroscopy and elemental analysis.

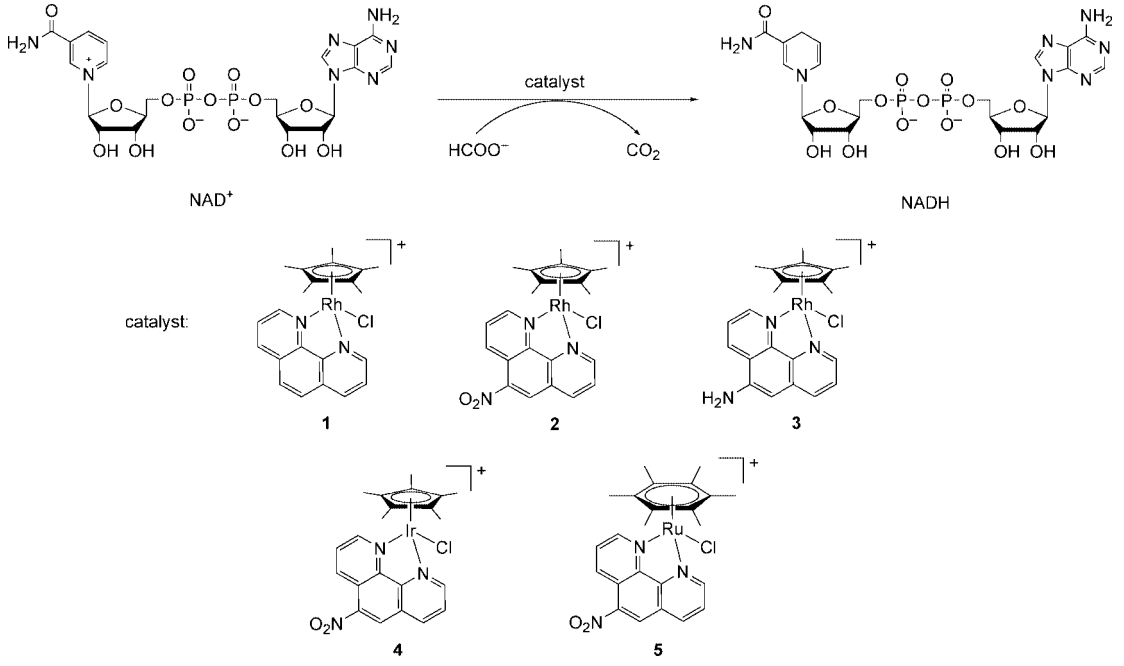
In all cases, the phenanthroline ligand is coordinated in the *N*,*N*-chelating fashion to the metal centre. In contrast to the known, symmetrical 1,10-phenanthroline complex **1**,[36] the new 5-nitro- and 5-amino-1,10-phenanthroline cations **2**, **3** and **4** are chiral, and compounds [**2**]Cl, [**3**]Cl and [**4**]Cl are produced as racemic mixtures.

Catalytic Reduction of NAD^+ to NADH in Aqueous Solution

Inspired by the pioneering studies of Steckhan[30] and Fish[33] on the use of (η^5-cyclopentadienyl)rhodium bipyridine complexes as catalysts for the regioselective reduction of NAD^+ models with the formate anion as the hydrogen source in aqueous solution, we studied this reaction catalysed by cations **1**–**4** as well as by the previously described complex $[(\eta^6\text{-}C_6Me_6)Ru(5\text{-}NO_2\text{-phen})Cl]^+$ (**5**),[37] which is known to be active for the reduction of ketones in water (Scheme 1).

Cations **1**–**5** were found to promote the reduction of NAD^+ to NADH in aqueous solution with sodium formate as the hydrogen donor (Table 1). The best results were obtained with rhodium complexes **1**–**3**, which led to TOFs ranging from 1500 to 2000 h^{-1} at 60 °C and pH = 7. In comparison with the analogous bipy complex $[(\eta^5\text{-}C_5Me_5)Rh(bipy)Cl]^+$ (TOF = 875 h^{-1}), commonly used as a catalyst for this reaction, phen analogue **1** is more than twice as active (TOF = 2000 h^{-1}) under the same conditions.

Ruthenium complex **5** shows a catalytic activity fifteen times lower than that observed with the related rhodium complex **2** (entries 6 and 21). The low activity of the ruthenium complex observed in this study is similar to the results recently published by Sadler et al. describing the use of (arene)(ethylenediamine)ruthenium complexes for the reduction of NAD^+ to NADH in aqueous solution at 37 °C

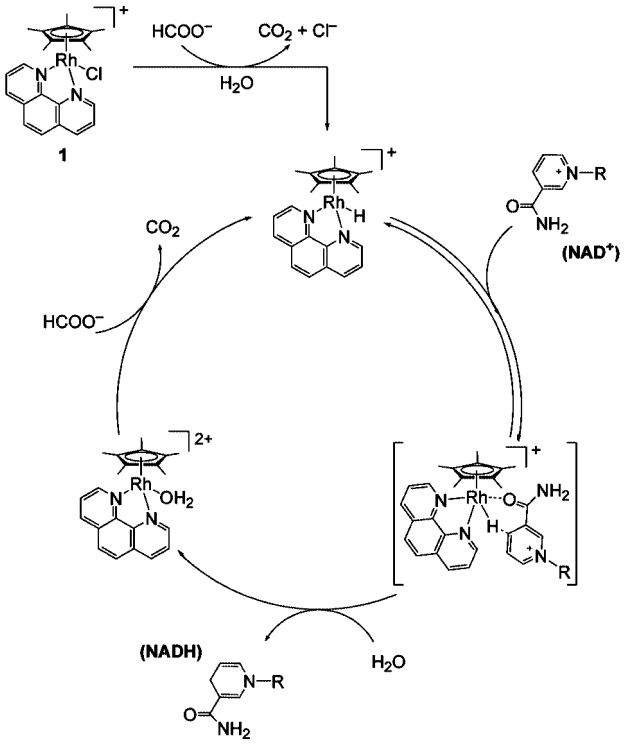


Scheme 1. Transfer hydrogenation of NAD^+ to NADH in aqueous solution catalysed by cationic chlorido complexes **1** to **5** by using the formate anion as the hydrogen source.

Table 1. Transfer hydrogenation of NAD^+ to NADH in aqueous solution by using the formate anion as the hydrogen source.[a]

Entry	Catalyst	n_s/n_c[b]	T[°C]	pH	Conversion [%] (Time [h])[c]	TOF [h^{-1}][c,d]
1	**1**	1000	38	7	100 (2.5)	560
2		1000	60	7	100 (0.5)	2000
3	**2**	15	25	7	100 (3)	19.5
4		15	38	7	100 (0.25)	30
5		50	38	7	100 (0.5)	100
6		100	38	7	100 (2.5)	150
7		500	38	7	100 (3.5)	380
8		1000	38	7	100 (4)	400
9		1000	60	7	100 (0.75)	1740
10		15	38	4[e]	100 (0.5)	29
11	**3**	1000	38	7	100 (4)	400
12		1000	60	7	100 (1)	1500
13	**4**	15	25	7	100 (5)	14.4
14		15	38	7	100 (2.5)	23
15		50	38	7	100 (4.5)	47
16		100	38	7	100 (7)	58
17		15	38	4[e]	100 (3)	22.5
18	**5**	15	25	7	35 (24)	1.5
19		15	38	7	70 (24)	6
20		50	38	7	50 (24)	8
21		100	38	7	20 (24)	10
22		15	38	4[e]	55 (24)	5.4
23	$[(\eta^5\text{-}C_5Me_5)Rh(bipy)Cl]^+$	1000	60	7	100 (2)	875

[a] Conditions: [NAD^+] = 8 mM, [$NaHCO_2$] = 350 mM; reactions carried out in 1 mL of phosphate buffer (pH 7). [b] Mol of substrate per mol of catalyst. [c] Determined by UV-absorption at 340 nm. [d] Turnover frequencies determined after 30 minutes and expressed in mol of product/(mol of metal·h). [e] Reactions carried out in phthalate buffer.



Scheme 2. Postulated catalytic cycle, based on the work of Fish, for the reduction of NAD^+ to NADH in aqueous solution with **1** as the catalyst.

and pH = 7.2.[38] Iridium complex **4** is also two times less active than the rhodium analogue **2** under the same conditions (entries 6 and 16). The results with varied pH demonstrate that the catalytic activity does not show any significant pH dependence.

According to the mechanistic scheme proposed by Fish et al. for the analogous bipy complexes,[33] cationic complex **1** is supposed to react with the formate anion to afford the corresponding hydrido complex, which can reduce NAD^+ to NADH (Scheme 2). The postulated catalytic cycle involves a transition state for hydride transfer from the rhodium centre to the pyridinium group, in which the NAD^+ and the metal hydride form a kinetically stable six-membered ring.

Electrochemical Behaviour of the Phenanthroline Complexes

The electrochemical behaviour of complexes **1**–**4** has been studied by cyclic voltammetry at a stationary platinum disc and by voltammetry at a rotating platinum disc electrode (RDE) by using acetonitrile solutions (analyte concentration: ca. 5×10^{-4} M) containing $Bu_4N[PF_6]$ (0.1 M) as the supporting electrolyte. Relevant data together with the parameters for the related Ru complexes[39] are summarised in Table 2.[40]

The redox response of phenanthroline complex **1** is shown in Figure 1. The first reduction occurs as a two-electron irreversible process (up to 500 $mV\,s^{-1}$), which is, however, fast and diffusion controlled ($i_{pa} \propto v^{1/2}$, $i_{lim} \propto \omega^{1/2}$). The associated oxidative peak (B) retains the diffusion control ($i_p \propto v^{1/2}$) but shows a peak current lower than that of the corresponding reduction wave (A). Such behaviour parallels that of the related cations $[L_nMCl(bipy)]^+$ [L_nM = $(\eta^5\text{-}C_5Me_5)Rh$, $(\eta^5\text{-}C_5Me_5)Ir$ and $(\eta^6\text{-arene})Ru$; bipy =

Table 2. Summary of the electrochemical data.[a]

Compound	E_p[V]	Reference
$[(\eta^5\text{-}C_5Me_5)RhCl(phen)]^+$ (**1**)	–1.32 (A), –1.10 (B), ≈ +0.64 (C)	this work
$[(\eta^5\text{-}C_5Me_5)RhCl(5\text{-}NO_2\text{-}phen)]^+$ (**2**)	–1.01/–0.93 (NO_2),[b] –1.43 (A), ≈ +0.64 (C)	this work
$[(\eta^5\text{-}C_5Me_5)RhCl(5\text{-}NH_2\text{-}phen)]^+$ (**3**)	–1.28 (A), –1.16 (B)	this work
$[(\eta^5\text{-}C_5Me_5)IrCl(phen)]^+$ (**4**)	–0.99 (A), –0.90 (B), ≈ +0.64 (C)	this work
$[(\eta^6\text{-}C_6Me_6)RuCl(phen)]^+$ (**5**)	–1.59 (A)	[39]
$[(\eta^6\text{-}C_6Me_6)RuCl(5\text{-}NO_2\text{-}phen)]^+$	–0.99 ($E^{\circ\prime}$ for NO_2)	[39]
$[(\eta^6\text{-}C_6Me_6)RuCl(5\text{-}NH_2\text{-}phen)]^+$	–1.58 (A)	[39]

[a] The potentials are given relative to the ferrocene/ferrocenium reference (see the Experimental Section for details). Peak potentials for irreversible processes were obtained at a scan rate of 100 mV s^{-1}. Definitions: $E^{\circ\prime} = \frac{1}{2}(E_{pa} + E_{pc})$, $\Delta E_p = E_{pa} - E_{pc}$. [b] E_{pc}/E_{pa} for the reversible reduction of the nitro group.

2,2′-bipyridine] and $[(\eta^5\text{-}C_5Me_5)MCl(bpym)]^+$ (M = Rh and Ir; bipym = 2,2′-bipyrimidine)[41–43] and can be explained by reductive removal of the chlorido ligand as shown in Equation (2).

$$[(\eta^5\text{-}C_5Me_5)M(phen)Cl]^+ + 2e^- \rightarrow [(\eta^5\text{-}C_5Me_5)M(phen)] + Cl^- \quad (2)$$

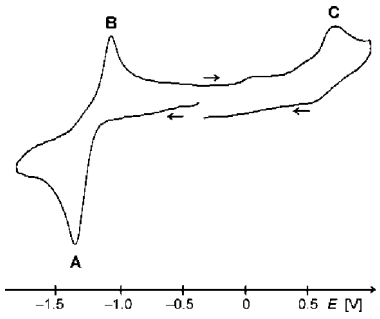


Figure 1. Cyclic voltammogram of **1** as recorded at a platinum disc electrode in acetonitrile solution at 100 mV s^{-1} scan rate. The potentials are given relative to the ferrocene/ferrocenium reference.

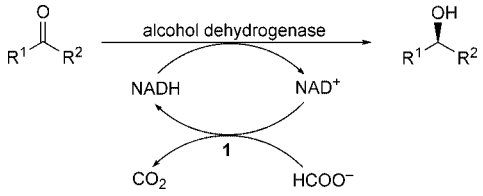
The neutral electrogenerated species $[(\eta^5\text{-}C_5Me_5)M(phen)]$ is probably rather unstable and becomes oxidised in a single step, giving rise to wave B. A broad wave (C), observed in the anodic region, can be attributed to oxidation of some decomposition product(s). However, the exact nature of this redox process remains unclear.

The presence of an amino group at the phenanthroline ligand in **3** has only a minor influence on the electrochemical behaviour, manifested mainly by a slight shift of the A and B waves to higher potentials and also by a diminished A–B separation. On the contrary, substitution with a nitro group markedly changes the redox response, as the nitro group is reduced first in a reversible, one-electron process ($–NO_2 + e^- \rightleftarrows –NO_2^{\cdot-}$), the potential of which is independent of the metal (Rh vs. Ir). Such an "inserted" redox step naturally influences the following one(s).

In the case of **2**, the metal-centred reduction occurs at –1.44 V (wave A), while for **5** only a broad wave at around –1.6 V could be detected. The associated counterwave (if any) is difficult to detect. This could explain the higher activity of rhodium catalyst **2** as compared with that found for ruthenium catalyst **5** in the reduction of NAD^+ to NADH described above, the more difficult-to-reduce species being less catalytically active.

Chemoenzymatic Enantioselective Reduction of Ketones

In light of the findings by Steckhan[22] and Schmid[1] on organometallic NADH regeneration for enzymatic ketone reductions, we studied the chemoenzymatic enantioselective transfer hydrogenation of 4-phenylbutan-2-one and acetophenone in aqueous solution. We used the NADH-dependent enzymes horse liver alcohol dehydrogenase (HLADH) or alcohol dehydrogenase from *Rhodococcus sp.* (S-ADH) and **1** as the NADH-regenerating catalyst with the formate anion as the hydrogen source (Scheme 3).



Scheme 3. Organometallic NADH regeneration for the stereoselective reduction of ketones with alcohol dehydrogenase.

The NADH-regenerating catalytic system with **1** as the catalyst was found to be active in combination with the two enzymes used (HLADH and S-ADH) for the enantioselective reduction of the test substrates (Table 3). The reaction proceeds with good to excellent enantioselectivity, producing predominantly the *S* enantiomer.

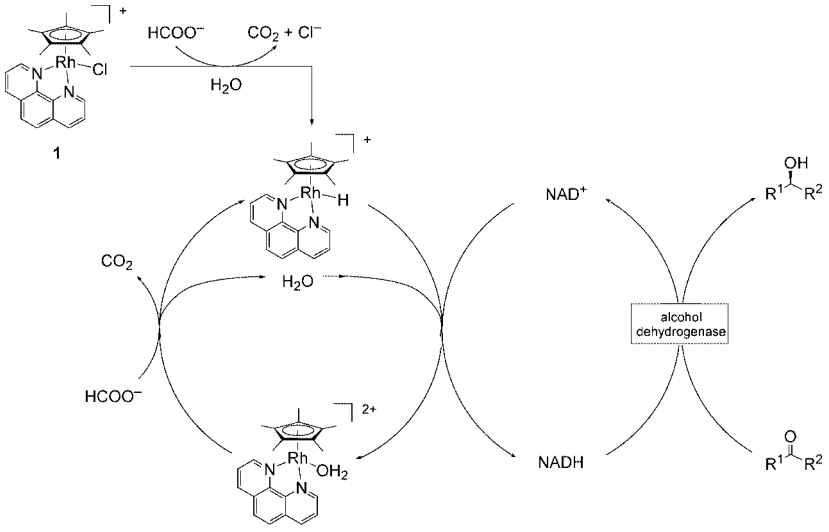
The results show the enantioselectivities to be similar to those found without the organometallic NADH regeneration catalyst with *ee* values up to 92 and 98%. However, the enzymatic activity with NADH regeneration is somewhat lower relative to enzymatic ketone reduction with excess NADH. This could be explained by a deactivation of the organometallic catalyst during the reaction, probably due to coordination of functional enzyme groups to the rhodium centre.

The mechanistic aspects of the combined organometallic–enzymatic catalysis are summarised in Scheme 4, which is a combination of Scheme 2 and Scheme 3. The organometallic intermediates $[(\eta^5\text{-}C_5Me_5)Rh(phenanthroline)H]^+$ and $[(\eta^5\text{-}C_5Me_5)Rh(phenanthroline)(OH_2)]^{2+}$ work hand-in-hand with the coenzyme intermediates NAD^+ and NADH to perform the enantioselective reduction of a ketone to give the corresponding alcohol, with aqueous sodium formate as hydrogen source and a dehydrogenase enzyme as chiral inducer.

Table 3. Chemoenzymatic enantioselective transfer hydrogenation of ketones with alcohol dehydrogenase and **1** as NADH-regenerating catalysts in aqueous solution.[a]

Entry	Ketone	Enzyme	Conc. of Rh [mM]	*t* [h]	Conversion [%][b]	*ee* [%][b]
1[c]	4-phenylbutan-2-one	HLADH	0	24	80	96
2[d]	4-phenylbutan-2-one	none	0.5	24	4	n.d.
3	4-phenylbutan-2-one	HLADH	0.5	24	62	92
4	4-phenylbutan-2-one	HLADH	0.1	24	47	88
5	4-phenylbutan-2-one	HLADH	0.01	24	1.2	n.d.
6	4-phenylbutan-2-one	HLADH	0.002	24	0.5	n.d.
7	acetophenone	HLADH	0.5	24	2	n.d.
8[c]	acetophenone	S-ADH	0	24	78	98
9[d]	acetophenone	none	0.5	24	8	n.d.
10	acetophenone	S-ADH	0.5	24	58	74
11	acetophenone	S-ADH	0.1	24	20	98

[a] Conditions: [NAD^+] = 1 mM, [$NaHCO_2$] = 100 mM, [ketone] = 33 mM, reactions carried out with 1 unit of alcohol dehydrogenase in 1 mL of phosphate buffer (pH 7) at 37 °C. [b] Determined by chiral HPLC analysis. [c] Conditions: [NADH] = 40 mM, [$NaHCO_2$] = 100 mM, [ketone] = 33 mM, reactions carried out with 1 unit of alcohol dehydrogenase in 1 mL of phosphate buffer (pH 7) at 37 °C. [d] Reaction carried out without HLADH or S-ADH and NAD^+.



Scheme 4. Catalytic cycle for the chemoenzymatic enantioselective transfer hydrogenation of ketones with **1** as NADH regenerating catalyst in aqueous solution.

Conclusions

In conclusion, we report here a series of five water-soluble rhodium, iridium and ruthenium complexes containing 1,10-phenanthroline and derivatives thereof as chelating ligands. All these complexes were found to catalyse the 1,4-regioselective reduction of NAD^+ to NADH in aqueous solution. TOF values up to 2000 h^{-1} have been obtained by using $[(\eta^5\text{-}C_5Me_5)Rh(phen)Cl]^+$ (**1**) as a catalyst at 60 °C and pH = 7. Furthermore, rhodium catalyst **1** has been found to be active as an NADH-regenerating catalyst for the chemoenzymatic enantioselective transfer hydrogenation of ketones in aqueous solution. Under biological conditions (37 °C, pH = 7), this system, which combines organometallic NADH regeneration and enzymatic reduction in aqueous solution, converts ketones into the corresponding chiral alcohols with good activities and enantioselectivities.

Experimental Section

General: All manipulations were carried out with freshly distilled solvents. The 5-amino-1,10-phenanthroline[44] and $[(\eta^6\text{-}C_6Me_6)Ru(5\text{-}NO_2\text{-}phen)Cl]^+$ (**5**)[37] were prepared according to the published methods. All other reagents were commercially available and were used without further purification. NMR spectra were recorded with a Bruker 400 MHz spectrometer by using sodium 2,2-dimethyl-2-silapentane-5-sulfonate in D_2O as an internal standard. Electrospray mass spectra were obtained in the positive-ion mode with an LCQ Finnigan mass spectrometer. Microanalyses were carried out by the Laboratoire de Chimie Pharmaceutique, Université de Genève (Switzerland).

Electrochemical measurements were carried out with a multipurpose polarograph PA3 interfaced to a Model 4103 XY recorder (Laboratorní přístroje, Prague) at room temperature by using a standard three-electrode cell with a rotating platinum disc electrode (RDE; 1 mm diameter) as the working electrode, platinum wire as

the auxiliary electrode and a saturated calomel electrode (SCE) as the reference electrode. The reference electrode was separated from the analysed solution by a salt bridge (0.1 M $Bu_4N[PF_6]$ in acetonitrile). The samples were dissolved in acetonitrile (Riedel-de Haën, purissimum p.a.), to give an analyte concentration of 5×10^{-4} M, and in 0.1 M $Bu_4N[PF_6]$ (Fluka, purissimum for electrochemistry). The solutions were purged with argon prior to the measurement and then kept under an argon blanket. Cyclic voltammograms were recorded at a stationary platinum disc electrode (scan rates 50–500 mV/s), while the voltammograms were obtained at a RDE (1000–2500 rpm, scan rate 20 mV/s). The redox potentials are given relative to the ferrocene/ferrocenium reference.

Preparation of Chlorido Complexes $[(\eta^5\text{-}C_5Me_5)M(N\cap N)Cl]^+$ (M = Rh, Ir and N∩N = phen, 5-NO_2-phen, 5-NH_2-phen): Two equivalents (0.30 mmol) of the appropriate phenanthroline donor were added to a suspension of $[(\eta^5\text{-}C_5Me_5)MCl_2]_2$ (M = Rh, Ir; 0.15 mmol) in dichloromethane (30 mL). The mixture was stirred for 3 h at room temperature, while the colour changed from dark orange to yellow-orange. After concentration to dryness, the residue was dissolved in water. This solution was filtered, and the filtrate was concentrated to dryness, which gave the product as a yellow powder in good yield.

$[(\eta^5\text{-}C_5Me_5)Rh(phen)Cl]Cl$ ([1]Cl): Yield: 74%, 80.8 mg. ^{1}H NMR (400 MHz, D_2O, 21 °C): δ = 1.70 (s, CH_3), 7.99 (s, CH), 8.05–8.12 (dd, $^3J_{H,H}$ = 5.1 Hz, $^3J_{H,H}$ = 8.1 Hz, CH), 8.67–8.71 (d, $^3J_{H,H}$ = 8.1 Hz, CH), 9.28–9.31 (d, $^3J_{H,H}$ = 5.1 Hz, CH) ppm. ^{13}C NMR (200 MHz, D_2O, 21 °C): δ = 8.32 [$C_5(CH_3)_5$], 97.9 [$C_5(CH_3)_5$], 126.63 (CH), 127.62 (CH), 130.98 (CH), 139.47 (CH), 146.08 (C), 155.62 (C) ppm. MS (ESI): *m*/*z* = 453 $[M]^+$. $C_{22}H_{23}Cl_2N_2Rh$ (489.24): calcd. C 54.01, H 4.74, N 5.73; found C 53.91, H 4.82, N 5.68.

$[(\eta^5\text{-}C_5Me_5)Rh(NO_2\text{-}phen)Cl]Cl$ ([2]Cl): Yield: 85%, 85.4 mg. ^{1}H NMR (400 MHz, D_2O, 21 °C): δ = 1.68 (s, CH_3), 7.99 (s, CH), 8.16–8.21 (quint, $^3J_{H,H}$ = 4.5 Hz, CH), 8.83–8.85 (d, $^3J_{H,H}$ = 8.2 Hz, CH), 8.96 (s, CH), 9.19–9.22 (d, $^3J_{H,H}$ = 8.7 Hz, CH), 9.36 (d, $^3J_{H,H}$ = 4.7 Hz, CH), 9.41 (d, $^3J_{H,H}$ = 4.8 Hz, CH) ppm. ^{13}C NMR (200 MHz, D_2O, 21 °C): δ = 8.52 [$C_5(CH_3)_5$], 98.8 [$C_5(CH_3)_5$], 123.62 (C), 127.63 (CH), 127.81 (C), 128.38 (CH), 128.41 (CH), 136.51 (CH), 141.71 (CH), 144.31 (C), 145.72 (C), 146.98 (C), 153.44 (CH), 155.14 (CH) ppm. MS (ESI): *m*/*z* = 498 $[M^+]$. $C_{22}H_{22}Cl_2N_3O_2Rh$ (534.24): calcd. C 49.46, H 4.15, N 7.87; found C 49.32, H 4.18, N 7.63.

$[(\eta^5\text{-}C_5Me_5)Rh(NH_2\text{-}phen)Cl]Cl$ ([3]Cl): Yield: 80%, 78.7 mg. ^{1}H NMR (400 MHz, D_2O, 21 °C): δ = 1.64 (s, CH_3), 6.60 (s, CH), 7.72–7.79 (dd, $^3J_{H,H}$ = 5.4 Hz, $^3J_{H,H}$ = 8.7 Hz, CH), 7.96–8.07 (m, $^3J_{H,H}$ = 8.8 Hz, CH), 8.54–8.58 (d, $^3J_{H,H}$ = 8.4 Hz, CH), 8.88–8.90 (d, $^3J_{H,H}$ = 4.4 Hz, CH), 9.22–9.24 (d, $^3J_{H,H}$ = 4.1 Hz, CH) ppm. ^{13}C NMR (200 MHz, D_2O, 21 °C): δ = 8.47 [$C_5(CH_3)_5$], 97.9 [$C_5(CH_3)_5$], 107.56 (CH), 126.52 (C), 126.80 (CH), 128.02 (CH), 128.91 (CH), 134.49 (CH), 136.00 (C), 138.41 (C), 145.54 (C), 148.94 (C), 151.81 (CH), 155.71 (CH) ppm. MS (ESI): *m*/*z* = 468 $[M]^+$. $C_{22}H_{24}Cl_2N_3Rh$ (504.26): calcd. C 52.40, H 4.80, N 8.33; found C 52.18, H 4.92, N 8.16.

$[(\eta^5\text{-}C_5Me_5)Ir(NO_2\text{-}phen)Cl]Cl$ ([4]Cl): Yield: 84%, 81.2 mg. ^{1}H NMR (400 MHz, D_2O, 21 °C): δ = 1.53 (s, CH_3), 8.05–8.09 (dd, $^3J_{H,H}$ = 5.3 Hz, $^3J_{H,H}$ = 8.8 Hz, CH), 8.94 (s, CH), 9.08–9.11 (d, $^3J_{H,H}$ = 8.7 Hz, CH), 9.22 (d, $^3J_{H,H}$ = 5.2 Hz, CH), 9.27 (d, $^3J_{H,H}$ = 5.4 Hz, CH) ppm. ^{13}C NMR (200 MHz, D_2O, 21 °C): δ = 8.14 [$C_5(CH_3)_5$], 90.72 [$C_5(CH_3)_5$], 124.02 (C), 127.75 (CH), 128.02 (C), 128.76 (CH), 128.83 (CH), 136.59 (CH), 141.64 (CH), 144.53 (C), 147.14 (C), 148.28 (C), 153.17 (CH), 154.76 (CH) ppm. MS (ESI): *m*/*z* = 588 $[M]^+$. $C_{22}H_{22}Cl_2IrN_3O_2$ (623.55): calcd. C 42.38, H 3.56, N 6.74; found C 42.24, H 3.67, N 6.54.

Catalytic NADH Regeneration: The reduction of NAD^+ (8 mM) catalysed by complexes [**1**–**5**]Cl with sodium formate (350 mM) as the hydrogen source was carried out in phosphate buffer (1 mL, pH 7) or in phthalate buffer (1 mL, pH 4). The conversion was determined by UV absorption at 340 nm. The pH was monitored with a pH meter (Mettler Toledo InLab® 413). Turnover frequencies were calculated for all the catalytic reactions from the conversions observed after 30 min for the hydrogenation reaction of NAD^+ to NADH. The results are summarised in Table 1.

Chemoenzymatic Hydrogenation of Ketones: The enzymatic transfer hydrogenation reactions of acetophenone or 4-phenylbutan-2-one (33 mM) were carried out in phosphate buffer (1 mL, pH 7) at 37 °C with 1 unit of alcohol dehydrogenase S-ADH or HLADH respectively, in the presence of NAD^+ (1 mM) and [**1**]Cl as NADH-regenerating catalyst and $NaHCO_2$ (100 mM) as the hydrogen source. The reactions without rhodium catalyst were performed with NADH instead of NAD^+ (40 mM), and the reactions without enzymatic reduction were performed without enzyme and NAD^+. The products were extracted with diethyl ether, filtered through silica and identified (and conversion and enantiomeric excess were determined) by HPLC on a Chiracel OD-H capillary column (hexane/2-propanol 9:10, 0.7 mL min^{-1}, 215 nm). The pH was monitored with a pH meter (Mettler Toledo InLab® 413).

Acknowledgments

This work was financially supported by the Swiss National Science Foundation and is a part of the long-term research projects supported by the Ministry of Education, Youth and Sports of the Czech Republic (project nos. MSM0021620857 and LC06070). The generous loan of ruthenium(III) chloride hydrate from the Johnson Matthey Research Centre is gratefully acknowledged.

[1] F. Holmann, A. Kleeb, K. Otto, A. Schmid, *Tetrahedron: Asymmetry* **2005**, *16*, 3512–3519.
[2] K. Everaere, A. Mortreux, M. Bulliard, J. Brussee, A. van der Gen, G. Nowogrocki, J. F. Carpentier, *Eur. J. Org. Chem.* **2001**, 275–291.
[3] J. Diez, M. P. Gamasa, E. Lastra, A. Garcia-Fernandez, M. P. Tarazona, *Eur. J. Inorg. Chem.* **2006**, 2855–2864.
[4] S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563.
[5] N. Dahlin, A. Bogevig, H. Adolfsson, *Adv. Synth. Catal.* **2004**, *346*, 1101–1105.
[6] W. He, P. Liu, B. L. Zhang, X. L. Sun, S. Y. Zhang, *Appl. Organomet. Chem.* **2006**, *20*, 328–334.
[7] P. F. Yan, C. H. Nie, G. M. Li, G. F. Hou, W. B. Sun, J. S. Gao, *Appl. Organomet. Chem.* **2006**, *20*, 338–343.
[8] W. He, B. L. Zhang, R. Jiang, P. Liu, X. L. Sun, S. Y. Zhang, *Tetrahedron Lett.* **2006**, *47*, 5367–5370.
[9] B. Z. Li, J. S. Chen, Z. R. Dong, Y. Y. Li, Q. B. Li, J. X. Gao, *J. Mol. Catal. A: Chem.* **2006**, *258*, 113–117.
[10] K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
[11] T. Abura, S. Ogo, Y. Watanabe, S. Fukuzumi, *J. Am. Chem. Soc.* **2003**, *125*, 4149–4154.
[12] X. H. Li, J. Blacker, I. Houson, X. F. Wu, J. L. Xiao, *Synlett* **2006**, 1155–1160.
[13] X. G. Li, X. F. Wu, W. P. Chen, F. E. Hancock, F. King, J. L. Xiao, *Org. Lett.* **2004**, *6*, 3321–3324.
[14] X. F. Wu, X. G. Li, F. King, J. L. Xiao, *Angew. Chem. Int. Ed.* **2005**, *44*, 3407–3411.

[15] J. Canivet, G. Labat, H. Stoeckli-Evans, G. Süss-Fink, *Eur. J. Inorg. Chem.* **2005**, 4493–4500.
[16] Y. Arakawa, N. Haraguchi, S. Itsuno, *Tetrahedron Lett.* **2006**, *47*, 3239–3243.
[17] L. Jiang, T. F. Wu, Y. C. Chen, J. Zhu, J. G. Deng, *Org. Biomol. Chem.* **2006**, *4*, 3319–3324.
[18] H. Y. Rhyoo, H. J. Park, W. H. Suh, Y. K. Chung, *Tetrahedron Lett.* **2002**, *43*, 269–272.
[19] Y. P. Ma, H. Liu, L. Chen, X. Cui, J. Zhu, J. E. Deng, *Org. Lett.* **2003**, *5*, 2103–2106.
[20] F. Wang, H. Liu, L. F. Cun, J. Zhu, J. G. Deng, Y. Z. Jiang, *J. Org. Chem.* **2005**, *70*, 9424–9429.
[21] D. S. Matharu, D. J. Morris, G. J. Clarkson, M. Wills, *Chem. Commun.* **2006**, 3232–3234.
[22] D. Westerhausen, S. Herrmann, W. Hummel, E. Steckhan, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1529–1531.
[23] A. Liese in *Technology Transfer in Biotechnology: from Lab to Industry to Production*, **2005**, *92*, 197–224.
[24] H. M. Zhao, W. A. van der Donk, *Curr. Opin. Biotechnol.* **2003**, *14*, 583–589.
[25] W. A. van der Donk, H. M. Zhao, *Curr. Opin. Biotechnol.* **2003**, *14*, 421–426.
[26] H. Groger, W. Hummel, S. Buchholz, K. Drauz, T. Van Nguyen, C. Rollmann, H. Husken, K. Abokitse, *Org. Lett.* **2003**, *5*, 173–176.
[27] F. Hollmann, A. Schmid, *Biocatal. Biotransform.* **2004**, *22*, 63–88.
[28] K. Vuorilehto, S. Lutz, C. Wandrey, *Bioelectrochemistry* **2004**, *65*, 1–7.
[29] R. Ruppert, S. Herrmann, E. Steckhan, *Tetrahedron Lett.* **1987**, *28*, 6583–6586.
[30] E. Steckhan, S. Herrmann, R. Ruppert, J. Thommes, C. Wandrey, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 388–390.
[31] R. Ruppert, S. Herrmann, E. Steckhan, *J. Chem. Soc. Chem. Commun.* **1988**, 1150–1151.
[32] J. Lutz, F. Hollmann, T. V. Ho, A. Schnyder, R. H. Fish, A. Schmid, *J. Organomet. Chem.* **2004**, *689*, 4783–4790.
[33] H. C. Lo, C. Leiva, O. Buriez, J. B. Kerr, M. M. Olmstead, R. H. Fish, *Inorg. Chem.* **2001**, *40*, 6705–6716.
[34] S. Ogo, O. Buriez, J. B. Kerr, R. H. Fish, *J. Organomet. Chem.* **1999**, *589*, 66–74.
[35] H. C. Lo, O. Buriez, J. B. Kerr, R. H. Fish, *Angew. Chem. Int. Ed.* **1999**, *38*, 1429–1432.
[36] U. Kolle, M. Grutzel, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 567–570.
[37] J. Canivet, L. Karmazin-Brelot, G. Süss-Fink, *J. Organomet. Chem.* **2005**, *690*, 3202–3211.
[38] Y. K. Yan, M. Melchart, A. Habtemariam, A. F. A. Peacock, P. J. Sadler, *J. Biol. Inorg. Chem.* **2006**, *11*, 483–488.
[39] P. Stepnicka, J. Ludvik, J. Canivet, G. Süss-Fink, *Inorg. Chim. Acta* **2006**, *359*, 2369–2374.
[40] E_{pa} and E_{pc} are anodic and cathodic peak potentials, respectively. Similarly, i_{pa} and i_{pc} denote the anodic and cathodic peak currents in cyclic voltammetry; i_{lim} is the limiting current in voltammetry at Pt-RDE, v is the scan rate, and ω is the rotation frequency of the disc electrode.
[41] M. Ladwig, W. Kaim, *J. Organomet. Chem.* **1991**, *419*, 233–243.
[42] M. Ladwig, W. Kaim, *J. Organomet. Chem.* **1992**, *439*, 79–90.
[43] W. Kaim, R. Reinhardt, M. Sieger, *Inorg. Chem.* **1994**, *33*, 4453–4459.
[44] D. Garcia-Fresnadillo, G. Orellana, *Helv. Chim. Acta* **2001**, *84*, 2708–2730.