Biomimetic Transfer Hydrogenation

DOI: 10.1002/anie.201210086

Bio-Inspired Catalytic Imine Reduction by Rhodium Complexes with Tethered Hantzsch Pyridinium Groups: Evidence for Direct Hydride Transfer from Dihydropyridine to Metal-Activated Substrate**

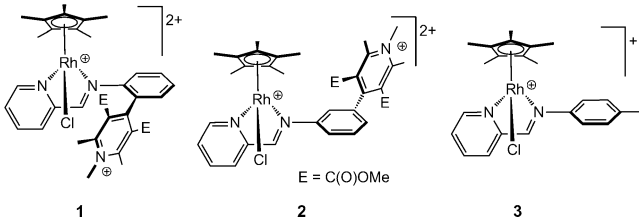
*Alex McSkimming, Mohan M. Bhadbhade, and Stephen B. Colbran**

Herein, we report a conceptually new approach to the catalytic reduction of unsaturated substrates, demonstrated for imine hydrogenation, based on mimicry of biological processes[1] in which hydride is directly transferred from dihydronicotinamide adenine dinucleotide (phosphate) (NAD(P)H) cofactor to an enzyme-activated substrate. NAD(P)H is Nature's hydride carrier.[2,3] In many (de)hydrogenase enzymes that catalyze direct hydride transfer to/from $NAD(P)^+$/NAD(P)H, the substrate is polarized and thus activated by binding to a metal ion.[4,5] Classic examples are alcohol dehydrogenases (Zn^{2+} active site)[4] and acetohydroxy acid isomeroreductase hydrogenases (with an $(Mg^{2+})_2$ or $(Mn^{2+})_2$ active site).[5]

Our aim in this research was to prepare and test a new design for a homogeneous catalyst in which an unnatural organo-transition-metal center is tethered to an organohydride donor (OHD). The design incorporates the main features of an (de)hydrogenase enzyme and its NAD(P)H cofactor into one molecule. We envisaged that the close proximity of cofacial, linked metal and OHD centers would facilitate both regeneration of the OHD through the intermediacy of metallo-hydride species and the rapid transfer hydride from the OHD to a metal-bound, and thus activated, unsaturated substrate.

We targeted a $[Cp^*Rh^{III}(NN)L]^{n+}$ (NN = diimine; L = halido, $n=1$; L = solvato co-ligand, $n=2$) complex, as these are the most commonly used catalysts for regeneration of NAD(P)H from $NAD(P)^+$.[6] Electrolytic reduction of $[Cp^*Rh^{III}(NN)L]^{n+}$ affords the corresponding Rh^I complex, which is rapidly protonated at low pH to give the active hydrido–Rh^{III} species for hydride transfer to $NAD(P)^+$.[6–9] Conveniently, catalytic regeneration of OHDs using $[Cp^*Rh^{III}(NN)L]^{n+}$ can be driven directly by electricity, by light and a photosensitizer, or by renewable chemical reductants, such as formate.[7–9] We employed a Hantzsch ester, such as 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (HEH), as the OHD center, because of their wide use as mimics for NAD(P)H in transfer hydrogenations of unsaturated substrates, such as imines or enones.[10,11] Typically, a Brønsted or Lewis acid catalyst is required to activate the substrate and to organize it and HEH for stereoselective hydride transfer.[10,11] Of note here is the recent disclosure by Zhou et al. on ruthenium-complex-catalyzed HEH regeneration using dihydrogen at high pressures for the asymmetric transfer hydrogenation of cyclic oximines catalyzed by a chiral phosphoric acid.[12] We believed that the flexible electron source and the mild reduction conditions for $[Cp^*Rh^{III}(NN)L]^{n+}$ catalysis of OHD regeneration would circumvent the demand for dihydrogen pressure and lead to a more convenient, greener, process. Moreover, substrate coordination and activation at the metal center would obviate the need for an expensive phosphoric acid catalyst.

To test our ideas, three complexes were synthesized: **1** and **2**, which have *ortho*- or *meta*-phenyl-bridged pyridinium (HE^+) and $[Cp^*Rh(NN)Cl]^+$ centers, respectively, and **3**,[13] which lacks an HE^+ substituent, as a control (Figure 1). The



1 2 3

Figure 1. Metal complexes examined as catalysts in this study.

N-methyl derivatives were targeted because reduction of the *N*-methylpyridinium cation is easier than reduction of the neutral pyridine conjugate of a non-*N*-methylated dihydropyridine. The new ligands and their rhodium complexes were synthesized using well-established methods (see the Supporting Information for details). Of note, **1** and **2** were made by selective oxidation of the corresponding *N*-methyl dihydropyridine-substituted complexes, **1**-H and **2**-H, with $(TEMPO)[BF_4]$.[14] A 1D-gradient-enhanced NOESY ^1H NMR experiment supports a structure for **1**-H in which the HEH-substituent and the chlorido ligand are oriented away from each other on opposite sides of the pyridylimine ligand (see the Supporting Information). UV/Vis spectra of **1**-H and **2**-H exhibit broad bands from the HEH moiety at 324 and 336 nm, respectively (this was also observed for the free

[*] A. McSkimming, Prof. S. B. Colbran
School of Chemistry, University of New South Wales
Sydney, NSW 2052 (Australia)
E-mail: s.colbran@unsw.edu.au
Dr. M. M. Bhadbhade
Mark Wainwright Analytical Centre, University of New South Wales
Sydney, NSW 2052 (Australia)

[**] This work was supported by ARC Discovery Projects (DP1301033514). We thank the Australian Synchrotron for access to crystallography facilities.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201210086.

ligand precursors; see the Supporting Information); these values are typical for Hantzsch 1,4-dihydropyridines.[15] In contrast, there are no bands above 300 nm in the UV/Vis spectra of **1** and **2**. In the FTIR spectra, **1** exhibits ester carbonyl stretching bands at 1752 and 1727 cm^{-1}. These values are appreciably higher than those for the carbonyl peak in the FTIR spectra of **1**-H at 1672 cm^{-1}, which is consistent with the positively-charged HE^+ ring in **1**. All complexes are air and moisture stable at ambient temperature in the solid state and in acetone solution.

Figure 2 presents views of **1** and **2** from the X-ray crystal structures of $[\mathbf{1}][PF_6]_2$·acetone and $[\mathbf{2}][PF_6]_2$. Both cations adopt the expected "piano-stool" geometry. The bond lengths and angles are all within reported ranges for similar $[Cp^*Rh(NN)L]^{n+}$ complexes.[7f,13] The chlorido ligand in **1** sits roughly atop the HE^+ ring and is 3.351 Å from the ring centroid (sum C+Cl van der Waals radii = 3.45 Å) with the closest Cl···C(HE^+) distances being 3.318 and 3.311 Å to C14 A and C15 A, respectively. The Cl···π-cation ring interaction seems to be stabilizing.[16] It may be deduced from the distinct ^1H and $^{13}C\{H\}$ NMR signals for the five methyl groups in **1** that a similar structure, with proximate HE^+ and Rh–Cl groups, is maintained in solution. In **2**, the *m*-phenyl spacer allows the HE^+ and Rh–Cl centers to orient away from each other, thus minimizing intramolecular steric interactions. According to our initial proposition (see above), the crystal structures suggest **1** should be a good transfer hydrogenation catalyst, whereas **2** should be a poor one.

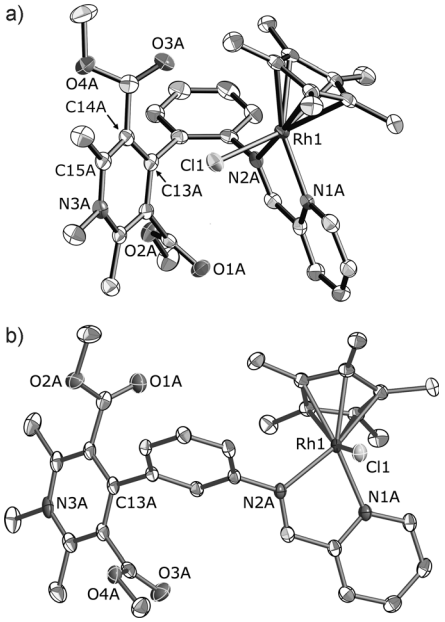
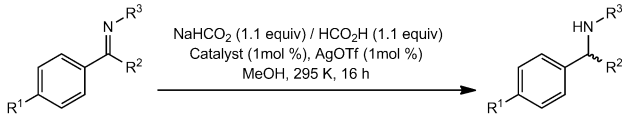


Figure 2. Views of a) **1** and b) **2** with thermal ellipsoids set at 50% (H atoms omitted for clarity). Selected distances [Å] and angles [°] for **1**: average Rh–C(Cp*) 2.164(4), Rh–N1 2.102(3), Rh–N2 2.175(3), Rh–Cl 2.3937(9), Rh···C13A 4.222; N1-Rh-N2 76.16(12), N1-Rh-Cl 85.94(8), N2-Rh-Cl 91.85(8). Selected distances [Å] and angles [°] for **2**: average Rh–C(Cp*) 2.164(3), Rh–N1 2.127(3), Rh–N2 2.115(3), Rh–Cl 2.4017(10), Rh···C13A 6.518; N1-Rh-N2 76.25(10), N1-Rh-Cl 88.01(8), N2-Rh-Cl 88.49(7).

Next **1**, **2,** and **3** (control) were screened as catalysts for the transfer hydrogenation of simple imines to the corresponding amines using formate ion (1.1 equiv) as the electron (hydride) source and formic acid (1.1 equiv) as a buffer. The results are presented in Table 1. The use of formic acid or formate alone gave poor results (entries 2 g and 2 h).

Table 1: Formate-driven transfer hydrogenations of imines using **1**, **2,** and **3** as catalysts.



Entry	R^1	R^2	R^3	Yield [%] with **1**[a]	Yield [%] with **2**[a]	Yield [%] with **3**[a]
1 a	OMe	H	4-MeC_6H_4	97 (95)	27	60
1 b				94[b]	38[b]	8[b]
2 a	Me	H	4-MeC_6H_4	>99 (98)	38	59
2 b				>99[c]	–	<2[c]
2 c				>99[d]		–
2 d				–		48[e]
2 e				(70)[f]		–
2 f				(90)[g]		
2 g				29[h]		
2 h				33[i]		
2 i				18[j]		
3	Cl	H	4-MeC_6H_4	98 (98)	9	25
4	NO_2	H	4-MeC_6H_4	29[k]	5[k]	3[k]
5	Me	Me	4-MeC_6H_4	89	9	5
6	Cl	Me	4-MeC_6H_4	79	<4	<3
7	Cl	H	*n*Bu	92	21	36
8	OMe	H	*n*Bu	94	<1	<1
9	Cl	H	Cy	93 (88)	13	30

[a] Yields were determined by ^1H NMR spectroscopy (values in parentheses are yields of products isolated by chromatography) and are for 16 h reactions. Each reaction was performed under a nitrogen atmosphere with solvent (10 mL) and substrate (0.24 mmol), unless otherwise noted. In all cases, no further conversion was observed upon extending the reaction time to 36 h. [b] No AgOTf added. [c] Performed in air. [d] Over Hg(*l*). [e] 1,2,6-Trimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5 mol%) added. [f] Imine not isolated, toluidine and tolualdehyde (1.2 equiv) added; [g] Imine not isolated, toluidine and tolualdehyde (2.2 equiv) added (5% 3° amine also isolated). [h] Only formic acid (1.1 equiv) added. [i] Only formate (1.1 equiv) added. [j] **1**-H used as catalyst. [k] MeOH (15 mL) used for solubility reasons. Cy = cyclohexyl.

From the results, **1** is by far the superior catalyst; with this catalyst the hydrogenations proceeded smoothly for most *N*-alkyl/aryl aldimines and ketimines to afford the corresponding amine, typically in >90% yield. The considerably lower conversion of the electron-deficient 4-nitrophenylimine (Table 1, entry 4), which by thermodynamic arguments should be the easiest to reduce, suggests that an inner-sphere reduction mechanism, in which the imine binds to the metal center, is operative. Initial optimization studies revealed that increasing concentrations of formate inhibit the reaction (see the Supporting Information), which is consistent with formate competively binding the metal center over the imine substrate. In contrast to **1**, **2** performed extremely poorly under identical conditions and, in most cases, was out performed by the control catalyst. In other

words, the HE^+ group in **2** actually acts to inhibit imine reduction.

A number of additional reactions offer insight into the catalysis. First, the addition of silver triflate (to sequester the chlorido ligand and thus ensure rapid coordination of formate to the rhodium center) was not necessary for imine hydrogenations using **1** (Table 1, entry 1a vs. 1b). However, the absence of silver triflate stifled the reaction when using the control catalyst **3**, which suggests that the chlorido ligand is less labile in this complex. This is likely due to the absence of labilizing intramolecular steric interactions.

Performing the reaction in an open flask under air (Table 1, entry 2b) did not hinder reactions using **1**. However, air almost completely halted reactions using the control catalyst **3**.

Metal–hydride complexes of the general formula $[Cp^*Rh(NN)H]^+$ are extremely air sensitive.[7b,d,9] The low catalytic activity of **3** in air most likely results from instability of the hydrido–Rh^{III} intermediate generated upon formate addition. The absence of air-sensitivity in transfer hydrogenation reactions using **1** as catalyst suggests that a hydrido–Rh^{III} intermediate does not form, or is very short lived.

Complex **1**-H was also screened for catalytic activity. Remarkably, this complex performed poorly (entry 2i), even below the activity of control complex **3**. Thus, **1**-H can not be an intermediate in the transfer hydrogenation of imines catalyzed by **1** (even though **1** is the product of hydride abstraction from **1**-H, see above). Likewise, attempts to reduce imines stoichiometrically with either **1**-H+AgOTf or **2**-H+AgOTf produced no amine.

We considered the possibility that **1** decomposes (because it is so sterically hindered) into a colloidal suspension of rhodium nanoparticles that catalyze imine hydrogenation. This possibility was ruled out by performing the reaction over rapidly stirred mercury (entry 2c); the mercury had no effect, therefore the catalysis is homogenous.[17] The addition of dimethyl-1,2,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate to reactions catalyzed by **3** provided no increase in yield (entry 2d). That is, the multi-component system containing a metal catalyst and an HEH proved ineffective (as was **2** with linked, but isolated, metal and HE^+ centers).

An attempt to bypass prior synthesis of the imine by direct reductive amination catalyzed by **1** met with some success. Reaction of 4-toluidine and 4-tolualdehyde (1.2 equiv) using the standard conditions gave the 2° amine in moderate yield (70%; entry 2e) with some toluidine remaining unreacted. Reaction of 4-toluidine with more 4-tolualdehyde (2.2 equiv) under the standard conditions using **1** as catalyst increased the yield of isolated 2° amine to 90% (entry 2f), with ca. 5% of the tertiary amine also isolated. These results suggest that the **1**-catalyzed reduction of aldehydes is slow relative to imine formation. Reduction of 4-chlorobenzaldehyde using the standard conditions listed in Table 1 gave ca. 76% of 4-chlorobenzyl alcohol for **1** and 8% for **3**. Attempted reduction of 4-chlorobenzophenone gave no conversion using **1** or **3**. Likewise, attempted reductive aminations of aliphatic ketones were unsuccessful.

To glean the standard turnover frequency (TOF°)[18] of **1** versus **3**, the times taken to convert ca. 50% of ditolylimine (Table 1, entry 2) into 2° amine were measured. This gave a TOF°(295 K) of $(66 \pm 24)\ h^{-1}$ for **1** and $(3.3 \pm 0.5)\ h^{-1}$ for **3** (reactions run three times). Although higher TOF°s have been reported for imine transfer hydrogenation reactions,[19] these results clearly demonstrate the superiority of **1** compared to **3**. The total turnover number (TTON) of **1** for the reduction of imine **2** was determined to be 179 ± 28 (reactions run five times with catalyst loadings of 0.1–0.5 mol%). This TTON value for **1** implies moderate catalyst stability under the conditions employed, and suggests ca. 1 mol% catalyst is required to achieve near-quantitative conversions.

The electrochemistry of **1**, **2**, and **3** is revealing. Cyclic voltammograms (CVs) of each complex were recorded and examples are presented in Figure 3. The primary reduction

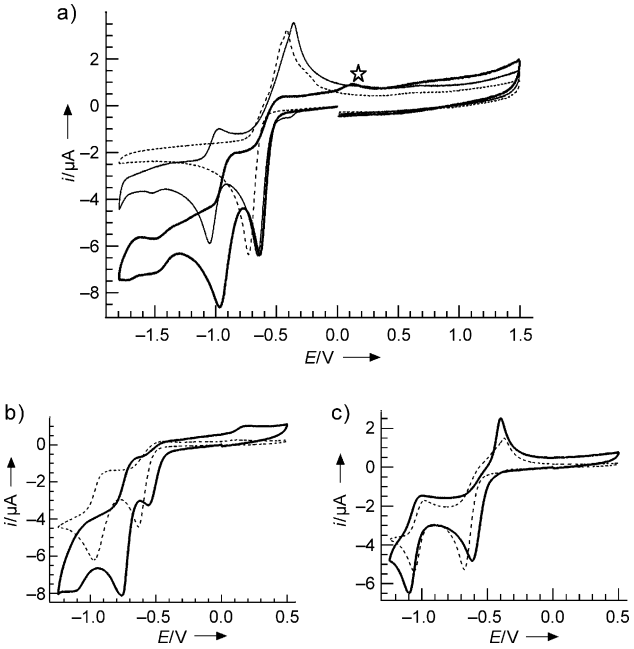


Figure 3. a) Cyclic voltammograms of **1** (▬), **2** (——), and **3** (-----). b) Cyclic voltammograms of **1** before (-----) and after (▬) addition of 50% (v/v) TEOA/TEOA·HBF_4 (0.1 M, pH 7) buffer in MeOH. c) As for (b), but with **2**. Conditions: $[(n\text{Bu})_4\text{N}][PF_6]$ (0.1 M) in acetonitrile at 298 K; glassy carbon mini-disk (1.0 mm diameter) working electrode; scan rate = 300 $mV s^{-1}$ for (a) and 100 $mV s^{-1}$ for (b) and (c); $E_{1/2}$(ferrocenium/ferrocene) = +0.47 V (and is +0.630 V vs. NHE).

process (at −0.63 V for **1**, at −0.66 V for **2** and at −0.72 V for **3**) is attributed to the two-electron reduction of the rhodium center concerted with scission of the Rh–Cl bond [Eq. (1); $L = Cl^-$], which characterizes reduction of such Rh^{III} complexes.[9] For **2** and **3**, the reverse sweep shows an anodic peak for the reverse processes [Eq. (2)]. The cathodic and anodic processes [Eqs (1) and (2)], are not an electrochemical couple, because a structural change accompanies the change from Rh^{III} to Rh^{I} (ECEC mechanism: the initial one-electron reduction triggers diffusion-limited disproportionation of the intermediate Rh^{II} species with concomitant Rh^{I}–L bond scission).[9]

$$[Cp^*Rh^{III}(NN)L]^{n+} + 2\,e^- \rightarrow [Cp^*Rh^{I}(NN)] + L \quad (1)$$

$$[Cp^*Rh^{I}(NN)] + L \rightarrow [Cp^*Rh^{III}(NN)L]^{n+} + 2\,e^- \quad (2)$$

CVs of **1** and **2** also show a second reduction couple with poor chemical reversibility (i_p^a/i_p^c = ca. 0.6 for both complexes) at ca. −1.0 V, which corresponds to the one-electron reduction of the HE^+ group to the neutral radical (Eq. (3)], which is unstable and consumed by radical coupling on the CV (ms) timescale.[20] The weak Nernstian couple at −1.4 V observed for **1** and **2**, but not for **3**, is attributed to the reduction of the Hantzsch dihydropyridine dimer formed by coupling of the radical from the previous HE^+-centered reduction.[20]

$$HE^+ + e^- \rightarrow HE^{\bullet} \quad (3)$$

Notably, in the CVs of **1**, the anodic peak for the re-oxidation of the Rh^I species shifts considerably to +0.12 V (indicated by a star in Figure 3a) and exhibits a marked decrease in current. The drop in current reveals that the Rh^I state is rapidly lost. Connectivity and the relative orientation of Rh and HE^+ units define the only difference between **1** and **2**. The different behavior upon reduction of **1**, as compared to **2** and **3**, must arise from the adjacent Rh–Cl and HE^+ centers in the former complex. Therefore, the decreased current for re-oxidation of the Rh^I center, suggests that the Rh^I center is oxidized by the adjacent HE^+ group. The shift in the re-oxidation peak for **1** (vs. **2**) of ca. 500 mV suggests increased thermodynamic stability of the Rh^I state in **1**. It is not clear why, although we suspect it has to do with stabilizing interactions between the rhodium center and the ester groups of the HE^+/HEH substituents.[7f]

Figure 3b,c compares CVs of **1** and **2** before and after addition of a pH 7 buffer. For **2** and **3** (not shown), the overall reduction chemistry is unchanged by the buffer: only small potential shifts and some broadening of the peaks is seen. In contrast, the addition of pH 7 buffer to **1** causes dramatic changes to the redox behavior of the complex. The CVs reveal lower current for the primary reduction at −0.52 V [Eq. (1)], and for the HE^+/HEH couple at −1.04 V, [Eq. (3)], and the appearance of a new irreversible peak at −0.76 V. The new peak corresponds to reduction of the Rh^{III}–H complex formed by rapid protonation of the Rh^I species, [Eqs (4) and (5)]. Catalytic evolution of dihydrogen [Eqs (6), (1) and (4)], may contribute to the current for this peak. This behavior has been thoroughly characterized for $[Cp^*Rh^I(NN)]^0$ species under protic conditions.[9]

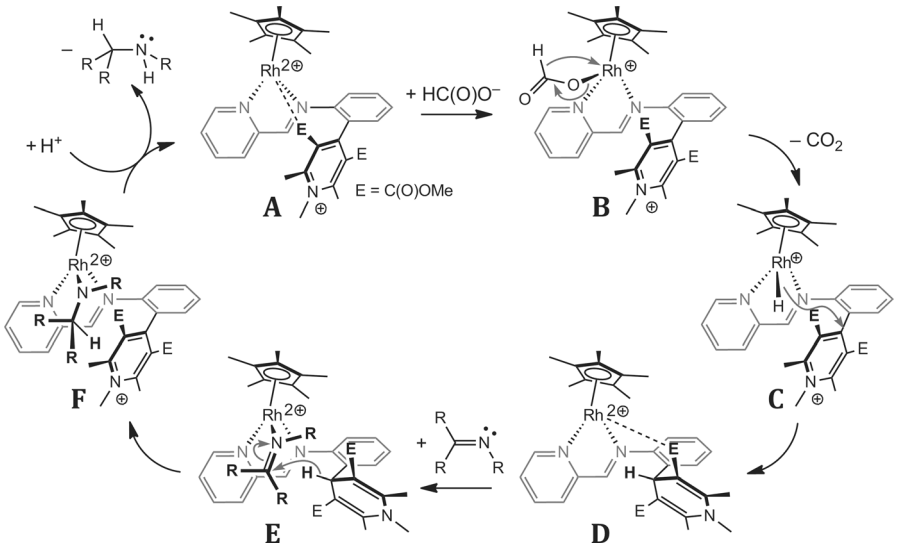
$$[Cp^*Rh^{I}(NN)] + H^+ \rightarrow [Cp^*Rh^{III}(NN)H]^+ \quad (4)$$

$$[Cp^*Rh^{III}(NN)H]^+ + 2\,e^- \rightarrow [Cp^*Rh^{I}(NN)] + H^- \quad (5)$$

$$[Cp^*Rh^{III}(NN)H]^+ + H^+ + L \rightarrow [Cp^*Rh^{III}(NN)L]^{n+} + H_2 \quad (6)$$

The CV response of **1** to the buffer is remarkable and important for a number of reasons. First, the marked drop in current for the reduction of HE^+ after addition of the buffer indicates that much of the HE^+ substituent has been reduced before the peak for its reduction is swept through. This can be due only to rapid hydride transfer in the hydrido–Rh^{III} species (**C**, Scheme 1). That is, transfer of hydride from the metal to the HE^+ group is rapid on the CV (ms) timescale, which explains the insensitivity of the reactions catalyzed by **1** to air (see above). UV/Vis spectroelectrochemical analysis shows that under protic conditions the primary (Rh-centered) reduction cleanly produces a species with a HEH center (λ_{max} = 354 nm; see the Supporting Information). Second, with pH 7 buffer, CVs of **1** show rapid formation of the hydrido–Rh^{III} complex [Eqs (4) and (5)], whereas those of **2** and **3** do not. Protonation of the Rh^I species from **1**, therefore, must be assisted by the proximate HE^+ group. Exactly how is not clear, but our hypothesis, and the basis for a theoretical study now underway, is that the ester groups are involved.

Based on the available evidence, we propose the tentative catalytic cycle depicted in Scheme 1 for the formate-driven reduction of imines catalyzed by **1**. Substitution of **A** (itself obtained from through dissociation or Ag^+ abstraction of the chlorido ligand in **1**) by formate ion affords **B**. Importantly, electrostatic effects ensure formate ion attacks Rh *syn* to the HE^+. Hydride transfer from the formato ligand to the metal then produces the Rh^{III}–H intermediate **C** and CO_2, which would be rapidly followed by hydride transfer to the adjacent HE^+ pyridinium group to give intermediate **D** with a HEH dihydropyridine group with the C4 hydrogen pointing directly at the Rh^{III} center (as opposed to **1**-H, which is inactive and



Scheme 1. Possible mechanism for the reduction of imines by formate catalyzed by **1**.

has the C4 hydrogen orientated away from the Rh^{III} center; see the Supporting Information). Alternatively, **D** could form directly from **B** by hydride transfer from the formato ligand to the HE^+ group.[21] Coordination of an imine gives **E**, in which the imine is activated for hydride attack. Coordination of a second equivalent of formate to Rh would compete with this step and lead to a dead-end Rh–H species, thus accounting for the lower yields with more equivalents of formate (see the Supporting Information). From **E**, intramolecular hydride transfer from the HEH moiety to the metal-activated imine affords the amido species **F**. Protonation of the amido ligand in **F** and loss of the amine product closes the catalytic cycle.

In summary, we have demonstrated a new bio-inspired approach to chemical reduction that operates under ambient conditions in air (even in a teacup; see the Supporting Information). Catalyst **1** has co-joined $[Cp^*Rh^{III}(NN)Cl]^+$ and Hantzsch HE^+/HEH centers that mimic the active site in a metallo-(de)hydrogenase enzyme and its $NAD(P)^+$/NAD(P)H OHD-cofactor, respectively. Crucial to the reduction of imines by **1** are: 1) the metal-catalyzed reduction of the HE^+ group to the dihydropyridine HEH, which leaves an open the site for imine coordination, and 2) back transfer of hydride from the HEH group to the metal-bound and activated imine. The results demonstrate that careful design of the multifunctional OHD-ligand is essential: the metal center and HE^+/HEH centers must abut one another for rapid intramolecular hydride transfer. We believe that this biomimetic design will have wide application in chemical reduction. For example, although this example is driven by formate ion, which is a renewable reductant,[22] it is also likely that these reductions can be driven electrochemically or photochemically.[7,8] We note that **1** is axially chiral. It remains to be seen whether the enantiomers of **1** or other chiral metal–OHD conjugates are active for asymmetric reduction. Also, the new catalyst design is not restricted to a Rh center or to a Hantzsch dihydropyridine OHD. There is a wide range of metal and OHD centers that may be co-joined and we anticipate some may be active for the reduction of more difficult substrates (including, perhaps, carbon dioxide and dinitrogen).

Finally, we note that this year, 2013, is the centenary of the award of the Nobel Prize for chemistry to Alfred Werner for his development of the coordination theory of transition metal complexes.[23] Werner's Nobel award was the first (and the only one for 72 years) in inorganic chemistry. Arthur Hantzsch was Werner's doctoral advisor, co-author of his doctoral thesis, and friend. He was also the discoverer of the synthetic route to the dihydropyridines that bear his name.[24] It has only taken 100 years to combine the work of doctoral advisor and student into one molecule. As we have demonstrated, provided the stereochemistry is correct (something that both Werner and Hantzsch would have appreciated and enjoyed)[25] novel catalytic behavior, well above and beyond that of the individual components, results.

Experimental Section

Standard conditions for the transfer hydrogenation of imines using $HCO_2H/NaHCO_2$ and **1**, **2**, and **3** as catalysts: Imine (0.240 mmol), metal catalyst (0.0024 mmol) and AgOTf (0.0026 mmol) were combined in a Schlenk flask and dissolved in MeOH (9.0 mL). The solution was deaerated with a steady stream of dinitrogen for ca. 10 min, at which point MeOH (1.0 mL) containing $HCO_2H/NaHCO_2$ (1:1, 0.530 mmol total) was injected. The solution was purged with dinitrogen for more 5 min and then the flask was sealed. Aliquots were taken at various intervals: the MeOH was removed, the residue taken up in $CDCl_3$, and the sample analyzed by ^1H NMR spectroscopy. For product isolation, the residue was subjected to column chromatography (60–200 μm silica support; ether/hexanes gradient as eluent). For catalyst **1**, AgOTf is unnecessary and the reactions may be run in an open vessel in air.

Received: December 18, 2012
Published online: February 26, 2013

Keywords: biomimetic catalysis · organo-hydride donor · redox-active ligands · rhodium · transfer hydrogenation

[1] V. K. K. Praneeth, M. R. Ringenberg, T. R. Ward, *Angew. Chem.* **2012**, *124*, 10374 – 10380; *Angew. Chem. Int. Ed.* **2012**, *51*, 10228 – 10234.

[2] J. Berg, J. Tymoczko, L. Stryer, *Biochemistry*, 6th ed., W. H. Freeman and Co., New York, **2007**.

[3] a) K. S. You, *Crit. Rev. Biochem.* **1985**, *17*, 313 – 451; b) N. Pollak, C. Dölle, M. Ziegler, *Biochem. J.* **2007**, *402*, 205 – 218.

[4] a) S. Hammes-Schiffer, S. J. Benkovic, *Annu. Rev. Biochem.* **2006**, *75*, 519 – 541; b) Z. D. Nagel, J. P. Klinman, *Chem. Rev.* **2006**, *106*, 3095 – 3118; c) D. Roston, A. Kohen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 9572 – 9577.

[5] a) R. Dumas, V. Biou, F. Halgand, R. Douce, R. G. Duggleby, *Acc. Chem. Res.* **2001**, *34*, 399 – 408; b) F. Proust-De Martin, R. Dumas, M. J. Field, *J. Am. Chem. Soc.* **2000**, *122*, 7688 – 7697.

[6] F. Hollmann, I. W. C. E. Arends, K. Buehler, *ChemCatChem* **2010**, *2*, 762 – 782.

[7] For seminal reports on NAD(P)H regeneration using [Cp*Rh(NN)L] catalysis, see: a) E. Steckhan, S. Herrmann, R. Ruppert, J. Thommes, C. Wandrey, *Angew. Chem.* **1990**, *102*, 445 – 447; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 388 – 390; b) E. Steckhan, S. Herrmann, R. Ruppert, E. Dietz, M. Frede, E. Spika, *Organometallics* **1991**, *10*, 1568 – 1577; c) D. Westerhausen, S. Herrmann, W. Hummel, E. Steckhan, *Angew. Chem.* **1992**, *104*, 1496 – 1498; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1529 – 1531; d) F. Hollmann, A. Schmid, E. Steckhan, *Angew. Chem.* **2001**, *113*, 190 – 193; *Angew. Chem. Int. Ed.* **2001**, *40*, 169 – 171; e) H. C. Lo, O. Buriez, J. B. Kerr, R. H. Fish, *Angew. Chem.* **1999**, *111*, 1524 – 1527; *Angew. Chem. Int. Ed.* **1999**, *38*, 1429 – 1432; f) H. C. Lo, C. Leiva, O. Buriez, J. B. Kerr, M. M. Olmstead, R. H. Fish, *Inorg. Chem.* **2001**, *40*, 6705 – 6716.

[8] For illustrative recent examples, see: a) H. K. Song, S. H. Lee, K. Won, J. H. Park, J. K. Kim, H. Lee, S. J. Moon, D. K. Kim, C. B. Park, *Angew. Chem.* **2008**, *120*, 1773 – 1776; *Angew. Chem. Int. Ed.* **2008**, *47*, 1749 – 1752; b) F. Hildebrand, C. Kohlmann, A. Franz, S. Lutz, *Adv. Synth. Catal.* **2008**, *350*, 909 – 918; c) S. H. Lee, J. Ryu, D. H. Nam, C. B. Park, *Chem. Commun.* **2011**, *47*, 4643 – 4645; d) S. H. Lee, H. J. Lee, K. Won, C. B. Park, *Chem. Eur. J.* **2012**, *18*, 5490 – 5495; e) S. H. Lee, D. H. Nam, C. B. Park, *Adv. Synth. Catal.* **2009**, *351*, 2589 – 2594; f) C. Leiva, H. C. Lo, R. H. Fish, *J. Organomet. Chem.* **2010**, *695*, 145 – 150.

[9] For (spectro-)electrochemical studies of [Cp*Rh(NN)L] complexes, see: a) M. Ladwig, W. Kaim, *J. Organomet. Chem.* **1991**, *419*, 233 – 243; b) U. Kölle, B. S. Kang, P. Infelta, P. Comte, M. Gratzel, *Chem. Ber.* **1989**, *122*, 1869 – 1880; c) C. Caix, S. Chardon-Noblat, A. Deronzier, J. C. Moutet, S. Tingry, *J. Organomet. Chem.* **1997**, *540*, 105 – 111; d) S. Chardon-Noblat, S. Cosnier, A. Deronzier, N. Vlachopoulos, *J. Electroanal. Chem.*

1993, *352*, 213 – 228; e) M. Ladwig, W. Kaim, *J. Organomet. Chem.* **1992**, *439*, 79 – 90.
[10] a) M. Rueping, J. Dufour, F. R. Schoepke, *Green Chem.* **2011**, *13*, 1084 – 1105; b) J. G. de Vries, N. Mrsic, *Catal. Sci. Technol.* **2011**, *1*, 727 – 735; c) C. Zheng, S. L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498 – 2518.
[11] a) L. Simon, J. M. Goodman, *J. Am. Chem. Soc.* **2008**, *130*, 8741 – 8747; b) O. Gutierrez, R. G. Iafe, K. N. Houk, *Org. Lett.* **2009**, *11*, 4298 – 4301; c) J. W. Yang, B. List, *Org. Lett.* **2006**, *8*, 5653 – 5655; d) S. L. Zhou, S. Fleischer, K. Junge, M. Beller, *Angew. Chem.* **2011**, *123*, 5226 – 5230; *Angew. Chem. Int. Ed.* **2011**, *50*, 5120 – 5124.
[12] a) Q. A. Chen, M. W. Chen, C. B. Yu, L. Shi, D. S. Wang, Y. Yang, Y. G. Zhou, *J. Am. Chem. Soc.* **2011**, *133*, 16432 – 16435; b) Q. A. Chen, K. Gao, Y. Duan, Z. S. Ye, L. Shi, Y. Yang, Y. G. Zhou, *J. Am. Chem. Soc.* **2012**, *134*, 2442 – 2448; c) F. Shi, L.-Z. Gong, *Angew. Chem.* **2012**, *124*, 11587 – 11589; *Angew. Chem. Int. Ed.* **2012**, *51*, 11423 – 11425.
[13] P. Govindaswamy, Y. A. Mozharivskyj, M. R. Kollipara, *Polyhedron* **2005**, *24*, 1710 – 1716.
[14] M. Shibuya, M. Tomizawa, Y. Iwabuchi, *J. Org. Chem.* **2008**, *73*, 4750 – 4752.
[15] a) R. A. Dommisse, F. C. Alderweireldt, *Bull. Soc. Chim. Belg.* **1973**, *82*, 441 – 445; b) R. F. Affeldt, R. S. Iglesias, F. S. Rodembusch, D. Russowsky, *J. Phys. Org. Chem.* **2012**, *25*, 769 – 777.
[16] a) D. Quiñonero, C. Garau, C. Rotger, A. Frontera, P. Ballester, P. A. Costa, P. M. Deya, *Angew. Chem.* **2002**, *114*, 3539 – 3542; *Angew. Chem. Int. Ed.* **2002**, *41*, 3389 – 3392; b) O. B. Berryman, V. S. Bryantsev, D. P. Stay, D. W. Johnson, B. P. Hay, *J. Am. Chem. Soc.* **2007**, *129*, 48 – 58; c) S. E. Wheeler, K. N. Houk, *J. Phys. Chem. A* **2010**, *114*, 8658 – 8664.
[17] J. A. Widegren, R. G. Finke, *J. Mol. Catal. A* **2003**, *198*, 317 – 341.
[18] S. Kozuch, J. M. L. Martin, *ACS Catal.* **2012**, *2*, 2787 – 2794.
[19] "Imino Reductions by Transfer Hydrogenation": M. Wills in *Modern Reduction Methods* (Eds.: P. Andersson, I. M. Munslow), Wiley-VCH, Weinheim, **2008**, chapter 11, pp. 271 – 296.
[20] F. T. Mcnamara, J. W. Nieft, J. F. Ambrose, E. S. Huyser, *J. Org. Chem.* **1977**, *42*, 988 – 993.
[21] H. Konno, K. Sakamoto, O. Ishitani, *Angew. Chem.* **2000**, *112*, 4227 – 4229; *Angew. Chem. Int. Ed.* **2000**, *39*, 4061 – 4063.
[22] A. Boddien, D. Mellmann, F. Gärtner, R. Jackstell, H. Junge, P. J. Dyson, G. Laurenczy, R. Ludwig, M. Beller, *Science* **2011**, *333*, 1733 – 1736.
[23] K. H. Ernst, F. R. W. P. Wild, O. Blacque, H. Berke, *Angew. Chem.* **2011**, *123*, 10970 – 10977; *Angew. Chem. Int. Ed.* **2011**, *50*, 10780 – 10787.
[24] A. Hantzsch, *Chem. Ber.* **1881**, *14*, 1637 – 1638.
[25] A. Hantzsch, A. Werner, *The Elements of Stereochemistry*, The Chemical Publishing Company, Easton, PA, **1901**.

