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Interplay between Hydrido/Dihydrogen and Amine/Amido Ligands in Ruthenium-Catalyzed Transfer Hydrogenation of Ketones

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This work describes the synthesis of three key intermediates of Noyori-type catalytic systems that are active precatalysts for the transfer hydrogenation of acetophenone. Isolation of the cationic chloro(dihydrogen) complex $[RuCl(H_2)(H_2NNPP)(PCy_3)][BArf_4]$ provides a facile synthetic route to the corresponding cationic and neutral hydrido complexes, and the series highlights the links between hydride/dihydrogen and amine/amido ligands in neutral and cationic species.

Transfer hydrogenation of ketones by using an alcohol, preferably isopropyl alcohol, is an interesting alternative to the classical hydrogenation process requiring the use of dihydrogen gas.[1] Following the pioneering work of Noyori on metal centers having in their coordination sphere a N ligand capable of acting as a hydrogen acceptor and/or donor, the literature now provides a wide variety of systems in which the "NH effect" is predominant.[1a,2] In this area, ruthenium is the metal of choice, despite major advances recently obtained with other metals, most remarkably with iron.[3] A number of systems aimed at developing new ligands favoring such a "NH effect" have been designed. Mechanistic information has been gained over the years, but the distinction between various pathways involving hydride or dihydride species and amine or amido ligands through inner- or outer-sphere mechanisms is still difficult. Moreover, the intermediacy of dihydrogen species remains scarce, despite their possible role in transfer hydrogenation reactions.[1a,2n,4]

Some of us have previously reported the synthesis of an aminophosphonium salt $[H_2NNHPP][Br]$ (with $H_2NNHPP = H_2NC_6H_4NHPPh_2CH_2PPh_2$), which after deprotonation and reaction with $RuCl_2(PPh_3)_4$ led to the formation of a dichloride complex incorporating a tridentate iminophosphoranephosphineamine ligand.[5] The corresponding hydridoamido species $RuH(HNNPP)(PPh_3)$ could then be obtained, and the two complexes were found to catalyze the transfer hydrogenation of acetophenone with moderate activity. We now describe a system based on the aminophosphonium salt, which allows us to isolate three key species that are active catalyst precursors for the transfer hydrogenation of ketones but, more importantly, a system highlighting the

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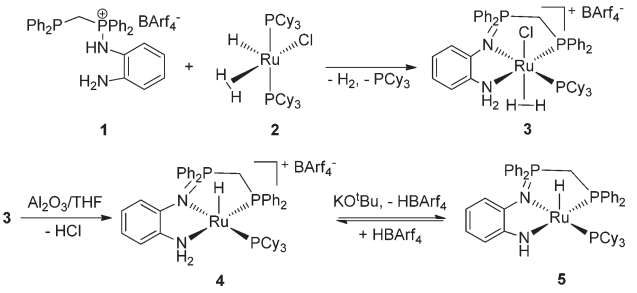
Scheme 1. Synthesis of the Three Catalyst Precursors **3**−**5**



links between hydride/dihydrogen and amine/amido ligands in neutral and cationic species.

The aminophosphonium $BArf_4$ salt $[H_2NNHPP][BArf_4]$ (**1**) was simply prepared from the bromine salt by anion exchange with $NaBArf_4$ ($BArf_4$ = $B(3,5\text{-}C_6H_3(CF_3)_2)_4$). **1** was deprotonated in situ by addition to the hydridochloro(dihydrogen) complex $RuHCl(H_2)(PCy_3)_2$ (**2**).[6] Dihydrogen evolution was observed, and the new cationic chloro(dihydrogen) complex $[RuCl(H_2)(H_2NNPP)(PCy_3)][BArf_4]$ (**3**) was isolated in very good yield (Scheme 1).

3 was characterized by elemental analysis, NMR, and X-ray crystallography. The dihydrogen ligand resonates at δ −10.23 with a $T_{1\ min}$ value of 28 ms at 500 MHz at 278 K. The amine ligand appears as an AB pattern at δ 5.99 and 4.72. The X-ray structure confirms the deprotonation of the initial NH group and shows a ruthenium in a pseudooctahedral geometry with a dihydrogen ligand trans to a chloride (Figure 1).

The dihydrogen ligand displays a short Hy1−Hy2 distance of 0.75(7) Å; however, the quality of the data is not sufficient to rely on such a short distance. Better evaluation can be obtained in such a case from the $T_{1\ min}$ NMR value, leading to an estimated distance of 0.90 Å in a fast-rotation regime.[7] There are very few chloro(dihydrogen) ruthenium complexes that have been characterized by X-ray diffraction.[8] In a very qualitative way, it seems reasonable to propose that **3** displays a dihydrogen acidity similar to that found in other $[RuCl(H_2)(P_2N_2)][X]$ compounds, as reported by Morris et al.[8a] As observed in other chlororuthenium complexes incorporating amino ligands,[8a] there is an intramolecular Cl1···Hy3N2 hydrogen bond with a Cl1···Hy3 distance of 2.63 Å.

Passing a tetrahydrofuran (THF) solution of **3** through an aluminum oxide column or adding 1 equiv of KO^tBu led to the isolation of a red solid $[RuH(H_2NNPP)(PCy_3)][BArf_4]$ (**4**), characterized as an unsaturated cationic hydrido complex by elemental analysis, NMR, and X-ray diffraction. The ^1H NMR spectrum shows a very shielded doublet of doublets at δ −31.15, in agreement with a hydride trans to a vacant site (see the Supporting Information). As depicted in Figure 1, the X-ray structure of **4** shows a square-pyramidal ruthenium center with a hydride in the apical position. **4** results from dehydrochlorination of **3**, and the geometrical parameters of the H_2NNPP ligand are very similar in the two complexes.

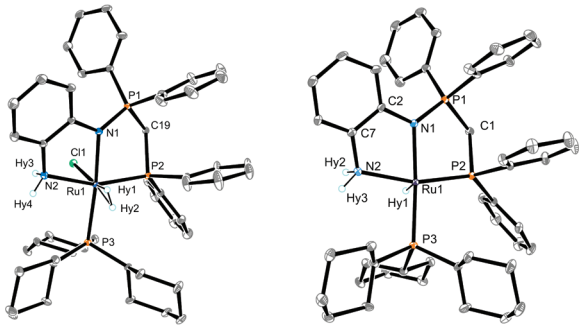


Figure 1. X-ray structures and selected bond distances (Å) and angles (deg) of cationic complexes **3** (left) and **4** (right) (anions omitted for clarity): Ru−N1, 2.1591(19), *2.137(3)*; Ru−N2, 2.164(2), *2.183(3)*; Ru−P2, 2.2864(6), *2.2254(9)*; Ru−P3, 2.3506(7), *2.2935(9)*; N1−Ru−N2, 77.40(8), *77.25(11)*; N1−Ru−P2, 85.19(5), *86.32(8)*; N2−Ru−P2, 161.14(6), *162.94(9)*; N1−Ru−P3, 173.11(5), *170.15(8)*; N2−Ru−P3, 96.51(6), *97.10(8)*; P2−Ru−P3, 101.22(2), *99.80(3)*.

It should be noted that the hydride Hy1 and the nitrogen proton Hy2 are pointing in the same direction and the distance of 2.61 Å could favor a subsequent concerted transfer.

Finally, the neutral hydrido(amido) complex RuH(HNNPP)(PCy_3) (**5**) could be obtained as a red powder by three synthetic pathways: either by adding 1 or 2 equiv of KO^tBu to **4** or **3**, respectively, or by passing a Et_2O solution of **3** through an aluminum oxide column and using THF as the final eluent. **5** is analogous to the PPh_3 complex previously reported,[5] with, in particular, a doublet of doublets in the hydride region at δ −24.00 and a singlet at δ 6.00 for the amido group. The PPh_3 complex was previously characterized by X-ray diffraction, and we propose a similar structure for our PCy_3 complex **5**.

Complexes **3**−**5** were found to be active precatalysts for the transfer hydrogenation of acetophenone using an isopropyl alcohol solution at 80 °C. The main results are summarized in Table 1.

Similar activities were observed at 80 °C for the three complexes tested under the same conditions (entries 1−3). Catalytic experiments carried out with compounds **3**−**5** always led to precipitation of a large quantity of **5** a few minutes after immersion of the reaction vessel into the 80 °C preheated oil bath. Conversions were high and reproducible (turnover frequency of around 9.3×10^{-3} s^{-1} at 50% conversion), although the concentration of the active species was significantly lower than that represented by the quantity of **3**−**5** used because of the insolubility of precipitated **5**. 96% conversion of acetophenone was observed reproducibly with all initiators **3**−**5**. In the absence of compounds **3**−**5**, transfer hydrogenation was still observed, but the activity was lower, with 29% conversion being obtained after 24 h (entry 4). Base-catalyzed hydrogenation of ketones is well documented.[9]

Compounds **4** and **5** are even active in the absence of sodium, although conversion is significantly lower (entries 5 and 6). A basic medium is required for hydride formation from compound **3**. However, any further role of the base remains so far unclear but might affect the acidity of the hydrogen atoms and thus hydrogen transfer. Conversion after 3 h was not improved by the presence of a dynamic

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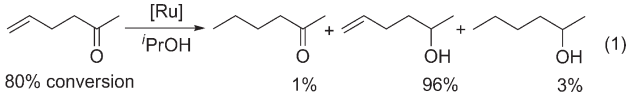
Table 1. Catalytic Transfer Hydrogenation of Acetophenone with Complexes **3**−**5** at 80 °C

		conversion (%)		
entry	catalyst	3 h	6 h	24 h
1[a]	**3**	84	94	96
2[a]	**4**	83	93	95
3[a]	**5**	80	91	96
4[b]		4	9	29
5[c]	**4**	4	8	79
6[c]	**5**	18	30	84
7[d]	**4**	22	40	82
8[e]	**4**	52	84	96

[a] Conditions: 100 equiv of acetophenone (146 μL, 1.25 mmol),10 equiv of sodium (2.9 mg, 0.125 mmol), 100 equiv of veratrole internal standard (160 μL, 1.25 mmol), and 1 equiv of precatalyst (0.0125 mmol) in 5 mL of ^{i}PrOH at 80 °C. [b] Conditions: same as those for footnote a but in the absence of compounds **3**−**5**. [c] Conditions: same as those for footnote a but in the absence of sodium. [d] Conditions: same as those for footnote a but with 6.25 mmol of acetophenone. [e] Conditions: same as those for footnote a but with the addition of PCy_3 (0.125 mmol).

dihydrogen atmosphere (3 bar). Conversions obtained over a 24 h period with **4** upon the addition of 500 equiv of acetophenone are shown in entry 7. The kinetics with precatalyst **4** were investigated, under the standard experimental conditions discussed. A semilogarithmic plot of ln [acetophenone] vs time (s) highlights a first-order dependence on the substrate concentration with no induction period ($k_{app} = 1.44 \times 10^{-4}$ s^{-1}; linear fit $R^2 = 0.997$). Temperature-dependent studies between 60 and 80 °C allow for extraction of the activation parameters $\Delta H^{\ddagger} = 71(3)$ kJ mol^{-1} and $\Delta S^{\ddagger} = -121(9)$ J K^{-1} mol^{-1} from the Eyring plot for the hydrogenation of acetophenone with **4** (see the Supporting Information). In addition, $\Delta G^{\ddagger}_{298} = 107(6)$ kJ mol^{-1} was obtained. The negative entropy indicates a highly ordered transition state with association of the complex and the substrate. The addition of PCy_3 (1 equiv or excess) only lowers the initial rate of hydrogenation, and high conversion is finally obtained after 24 h (96%; entry 8), thus ruling out the dissociation of PCy_3 as a key event in the catalysis. In order to gain some information on chemoselectivity, the hydrogenation of 5-hexene-2-one was tested by using complex **4** as a precatalyst in an isopropyl alcohol solution at 80 °C, under conditions analogous to those discussed in Table 1, footnote a. A mixture of hydrogenation products was obtained after 6 h (eq 1). The predominant species, 5-hexen-2-ol, as characterized by ^{1}H and ^{13}C NMR, gas chromatography−mass spectrometry (GC−MS), and GC indicates preferential hydrogenation of the ketone functionality with **4**.



(1)

We have performed a few stoichiometric reactions on the NMR scale in order to gain some more mechanistic information. We found that a species analogous to **4**, but with $[O^{i}Pr]^{-}$ in place of $[BArf_4]^{-}$, was readily formed upon the addition of isopropyl alcohol to **5**, as shown by ^{1}H and ^{31}P NMR data. Compound **5** also yields compound **4** upon reaction with 1 equiv of $HBArf_4$ [$HBArf_4 = Arf_4B^{-}(Et_2O)_2H^{+}$] at ambient temperature. **4** is stable with excess $HBArf_4$ after prolonged time periods in solution. Notably, compounds **4** and **5** did not react with acetophenone in THF-d_8 at ambient temperature or at 55 °C. No change in the ^{1}H and ^{31}P NMR spectra could be seen when monitoring the reaction of **4** in the presence of acetophenone, isopropyl alcohol, and sodium at ambient temperature or 55 °C over a period of 1.5 h, but phenylethylethanol was produced (^{1}H NMR and GC). Notably also, **5** is stable in the presence of ^{i}PrONa, whereas **4** leads to the formation of **5** when exposed to ^{i}PrONa, both at room temperature and at 55 °C. No evidence for the intermediacy of an alkoxide species could be demonstrated during all of our mechanistic investigations. Finally, an aliquot of the catalytic mixture with compound **4** as the catalyst precursor was taken after 2 h and analyzed by NMR at ambient temperature. A large quantity of **5** was observed as a precipitate, and no other species could be detected by ^{31}P NMR.

In conclusion, isolation of the chloro(dihydrogen)amino cationic complex **3** prior to formation of the hydridoamino cationic complex **4** and finally the neutral hydridoamido complex **5** provides useful insight into key intermediates of Noyori-type catalytic systems. The three complexes act as active precursors for the transfer hydrogenation of acetophenone. All of our observations are consistent with a transfer hydrogenation pathway and rule out a dihydrogen hydrogenation pathway, as quoted by Morris et al.[1a] We have shown that dehydrochlorination is readily achieved from the dihydrogen complex **3**. In this chloro(dihydrogen) complex, the dihydrogen ligand is more acidic than that in a corresponding hydrido(dihydrogen) species because the acidity of the dihydrogen ligand is highly dependent on the withdrawing properties of the trans ligand.[7] In contrast, subsequent deprotonation of the amino ligand in **4** is preferred, leading to formation of the neutral amido complex **5**. Remarkably, reprotonation of **5** to **4** is easily achieved in the presence of isopropyl alcohol, a key event related to the catalytic transfer hydrogenation system. No other intermediate could be observed during the course of the catalytic reaction. All of the experimental data that we have are in favor of a TOL mechanism,[1a] transfer hydrogenation with outer-sphere hydride transfer assisted by the ligand.

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Supporting Information Available: Full details of the synthesis and characterization of **3**−**5**, standard catalytic procedures, kinetic data, and X-ray crystallographic data in CIF format for **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.