Notes

Self-Assembled Bidentate Ligands for Ruthenium-Catalyzed Hydration of Nitriles

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Summary: Novel bis(acetylacetonato)ruthenium(II) complexes bearing the 6-diphenylphosphino-N-pivaloyl-2-aminopyridine and 3-diphenylphosphinoisoquinolone ligands were synthesized. Molecular structures of these complexes were studied in solution and also in the solid state, and unusual hydrogen-bonding patterns were identified. The prepared compounds constitute active catalysts for the hydration of nitriles to amides under neutral conditions.

Introduction

Selective hydration of nitriles to amides represents an example of an industrially important atom economic reaction.[1] A variety of transition-metal complexes have been investigated as homogeneous catalysts for this transformation.[2] Among them, Murahashi's ruthenium system[3] and Parkins's platinum complexes[4] are especially effective. More recently, Oshiki and co-workers have described the *cis*-Ru(acac)$_2$(PPh$_2$py)$_2$ complex (acac = acatylacetonato, PPh$_2$py = 2-diphenylphosphinopyridine) as an excellent catalyst for hydration of nitriles to amides under neutral conditions.[5] The proposed mechanism postulated the activation of the nitrile by coordination to a vacant site of the metal (formed by $\eta^2 \rightarrow \eta^1$ acac isomerization). Furthermore, it was suggested that nucleophilic addition of water is promoted via hydrogen bonding to the PPh$_2$py ligand (Scheme 1). This mechanism is an example of bifunctional catalysis, which involves the metal ion acting as a Lewis acid and the ligand acting as a Lewis base and directing the attack of water.[6,7]

During the course of our investigations on the formation of bidentate ligands via self-assembly, we have recently reported the construction of homodimeric[8] and heterodimeric[9] bidentate ligands based on complementary hydrogen bonding between formally monodentate ligands. An adenine/thymine base pair analogous system—the aminopyridine (**1**)/isoquinolone (**2**) platform (Scheme 2)—proved to be particularly useful.

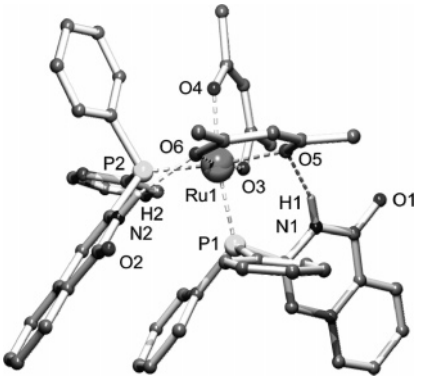
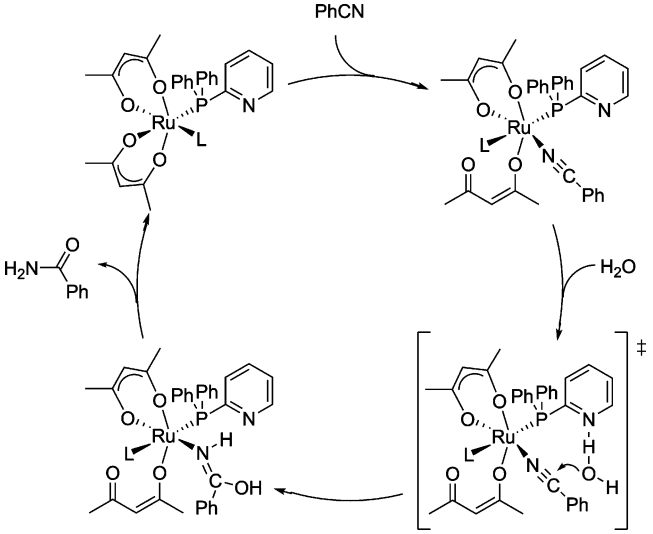


Figure 1. Molecular structure of complex **3**.

Scheme 1. Proposed Mechanism of the Catalytic Hydration of Benzonitrile.



From ligand libraries based on this self-assembly platform, highly active and regioselective rhodium catalysts for the hydroformylation of terminal alkenes[9] as well as for a highly enantioselective asymmetric hydrogenation[10] were identified. Furthermore, ruthenium complexes of the general structure CpRu(MeCN)(**1**^{x})(**2**^{y}) were identified as active catalysts for a

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(1) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.
(2) For a recent review on metal-catalyzed nitrile reactions, see: Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771.
(3) (a) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521. (b) Murahashi, S.-I.; Naota, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1805.
(4) (a) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657. (b) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A* **2000**, *160*, 249.
(5) Oshiki, T.; Yamashita, H.; Sawada, K.; Utsunomiya, M.; Takahashi, K.; Takai, K. *Organometallics* **2005**, *24*, 6287.
(6) Grotjahn, D. B. *Chem.—Eur. J.* **2005**, *11*, 7146.
(7) For an alternative mechanism of Ru-catalyzed hydration of nitriles see: Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225.
(8) Breit, B.; Seiche, W. *J. Am. Chem. Soc.* **2003**, *125*, 6608.
(9) Breit, B.; Seiche, W. *Angew. Chem.* **2005**, *117*, 1666; *Angew. Chem., Int. Ed.* **2005**, *44*, 1640.

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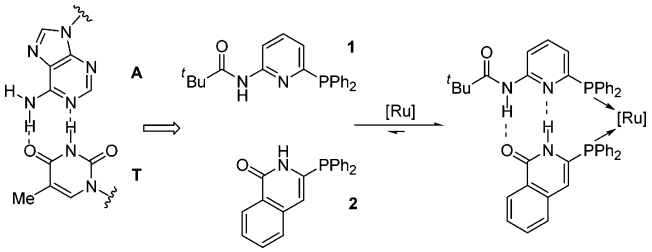
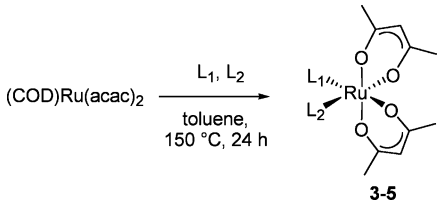
Scheme 2. Self-Assembly through Hydrogen Bonding of Adenine/Thymine and Aminopyridine/Isoquinolone Ligand Systems[a]



[a] Only the NH···O hydrogen bond is observed in the current work.

Table 1. Preparation of Bis-phosphine Ruthenium Complexes 3−5



L_1	L_2	isolated yield (%)
2	**2**	**3** (87)
2	**1**	**4** (70)
1	**1**	**5a**/**5b** (n.d.)

Table 2. Selected Bond Distances (Å) and Angles (deg) for 3

O(3)−Ru(1)	2.047(2)	O(3)−Ru(1)−O(5)	173.24(10)
O(4)−Ru(1)	2.094(2)	O(4)−Ru(1)−P(1)	168.73(7)
O(5)−Ru(1)	2.091(2)	O(5)−Ru(1)−P(2)	174.45(7)
O(6)−Ru(1)	2.072(2)	P(1)−Ru(1)−P(2)	99.55(3)
P(1)−Ru(1)	2.2847(9)		
P(2)−Ru(1)	2.2852(9)		

highly regioselective *anti*-Markovnikov hydration of terminal alkynes to give the corresponding linear aldehydes.[11]

We assume that during the course of this reaction the hydrogen-bonding network may serve a dual role: first emulation of a bidentate ligand situation to increase the binding constant of the phosphine ligands, leading to catalyst stabilization, and, second, activation of a water molecule via hydrogen bonding. Accordingly, we reasoned that metal complexes derived from our self-assembly ligand system may also serve as a "hydration" catalyst for other multiple bonds.

Herein we report on the synthesis of new bis(acetylacetonato)-ruthenium(II) complexes bearing the aminopyridine/isoquinolone ligands and their application as homogeneous catalysts for the hydration of nitriles.

Results and Discussion

Treatment of Ru(1,5-COD)(acac)$_2$[12] with 2 equiv of 6-diphenylphosphino-*N*-pivaloyl-2-aminopyridine (**1**), 3-diphenylphosphinoisoquinolone (**2**), or a 1:1 mixture of both in toluene at 150 °C afforded the corresponding bis-phosphine ruthenium complexes (Table 1).

Complex **3** was isolated by column chromatography as a yellow microcrystalline solid in good yield. The ^{1}H NMR spectrum of **3** in $CDCl_3$ at room temperature showed resonances at $\delta = 1.66$ (s) and 1.94 (s) for the protons of two nonequivalent methyl groups. The ^{31}P NMR of **3** in $CDCl_3$ at room temperature showed a singlet at $\delta = 55.2$. This is consistent with a symmetrical octahedral structure having both phosphine ligands *cis*-coordinated. The low-field shift of the isoquinolone NH signal (^{1}H NMR $\delta = 11.43$ (bs)) suggests that these hydrogen atoms are involved in hydrogen bonding.

Table 3. Hydrogen Bonding in 3, Selected Bond Distances (Å) and Angles (deg)

N−H···O	*d*(N−H)	*d*(H···O)	*d*(N···O)	∠(NHO)
N(1)−H(1)···O(5)	0.88	1.95	2.771(4)	155.6
N(2)−H(2)···O(6)	0.88	1.98	2.804(4)	155.5

Table 4. Selected Bond Distances (Å) and Angles (deg) for 4

O(3)−Ru(1)	2.0654(18)	O(6)−Ru(1)−O(3)	171.82(7)
O(4)−Ru(1)	2.1046(16)	O(4)−Ru(1)−P(1)	175.01(5)
O(5)−Ru(1)	2.0802(18)	O(5)−Ru(1)−P(2)	168.64(5)
O(6)−Ru(1)	2.0600(18)	P(1)−Ru(1)−P(2)	98.40(2)
P(1)−Ru(1)	2.2741(7)		
P(2)−Ru(1)	2.2953(7)		

Table 5. Hydrogen Bonding in 4, Selected Bond Distances (Å) and Angles (deg)

N−H···O	*d*(N−H)	*d*(H···O)	*d*(N···O)	∠(NHO)
N(1)−H(1)···O(3)	0.88	1.95	2.749(3)	161.6
N(3)−H(3)···O(1)	0.88	2.08	2.956(3)	173.6

In addition, the molecular structure of complex **3** has been determined by X-ray diffraction methods. Suitable single crystals were obtained by slow evaporation of the concentrated $CHCl_3$ solution at room temperature. X-ray crystallographic analysis confirmed that **3** is a mononuclear complex with distorted octahedral coordination geometry and the phosphine ligands are *cis*-coordinated (Figure 1). The structural parameters for the Ru(acac)$_2$(PAr$_3$)$_2$ unit (Table 2) are comparable to those reported for *cis*-Ru(acac)$_2$(PPh$_2$py)$_2$.[5] Both isoquinolone ligands are involved in hydrogen bonding with the oxygen atom of the acetylacetonate ligand (Figure 1, Table 3).

When employing a 1:1 mixture of the complementary ligands **1** and **2**, the exclusive formation of the heterocomplex **4** was observed; this was confirmed by mass spectrometry, NMR, and X-ray crystallography. Thus, the MS ESI+ spectrum showed the presence of ions at $m/z = 892$ ([**4** − acac]$^+$, 100%), 1014 ([**4** + Na]$^+$, 75%). The ^{31}P NMR spectrum of **4** in $CDCl_3$ at room temperature displayed an AB spin system with a $^2J_{P-P}$ coupling constant of 33.8 Hz (Figure 2). This confirms the presence of two nonequivalent phosphine ligands coordinated

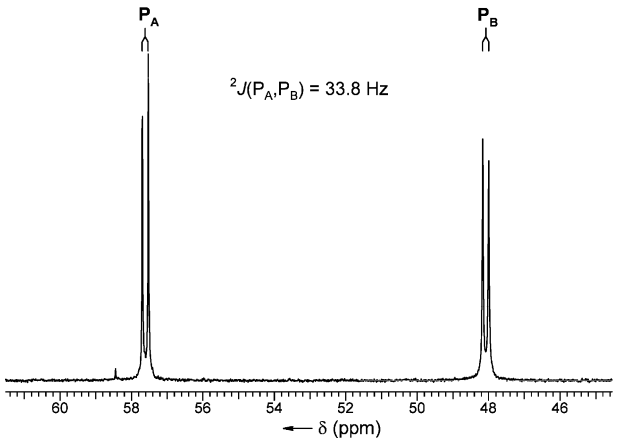


Figure 2. ^{31}P NMR spectrum of **4** in $CDCl_3$ solution.

(10) Weis, M.; Waloch, C.; Seiche, W.; Breit, B. *J. Am. Chem. Soc.* **2006**, *128*, 4188.
(11) Chevallier, F.; Breit, B. *Angew. Chem.* **2006**, *118*, 1629; *Angew. Chem., Int. Ed.* **2006**, *45*, 1599.
(12) Powell, P. *J. Organomet. Chem.* **1974**, *65*, 89.

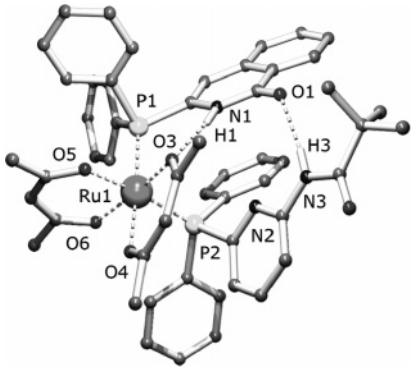


Figure 3. Molecular structure of complex **4**.

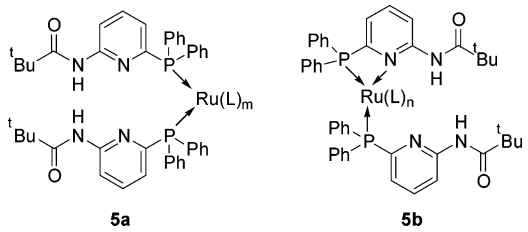


Figure 4. Proposed molecular structure of complexes **5a** and **5b**.

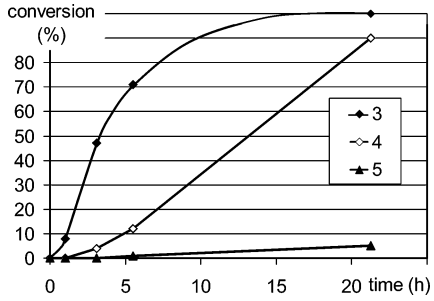


Figure 5. Catalytic hydration of 4-methylbenzonitrile. Reaction conditions: 4-methylbenzonitrile (1 mmol); catalyst **3**, **4**, **5** (10 μmol); H_2O (2 mmol); DME (1 mL), 150 °C.

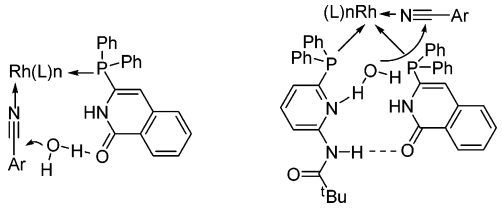


Figure 6. Hypothetical structures, directing of the nuclephilic attack of water.

to the same metal center. The ^{1}H NMR spectrum of **4** in $CDCl_3$ at room temperature showed resonances at $\delta = 10.71$ (s) and 12.05 (d) for the aminopyridine and isoquinolone NH, respectively. The low-field shift of these signals suggests that these hydrogen atoms are involved in hydrogen bonding.

A final confirmation of the molecular structure of **4** could be gained from X-ray crystallography (Figure 3). Good-quality crystals for X-ray diffraction were obtained by slow diffusion of *n*-hexane into the concentrated $CHCl_3$ solution. Thus, the two complementary phosphine ligands are *cis*-coordinated in a distorted octahedral coordination geometry at the ruthenium center (Table 4). Hydrogen bonding is observed between the amide group of the aminopyridine ligand **1** and the isoquinolone (**2**) oxygen (N3−H3···O1). The isoquinolone N−H is hydrogen bound to an oxygen atom of the acetylacetonate (N1−H1··· O3) (Figure 3, Table 5). The pyridine nitrogen (N2) of the ligand **1** is not involved in the binding to the isoquinolone NH and so is potentially available for the proposed activation of a water molecule.

The reaction of 2 equiv of ligand **1** with the complex Ru(1,5-COD)(acac)$_2$ afforded a 1:1 mixture of two ruthenium complexes, **5a** and **5b**, which could not be separated (Figure 4). The ^{31}P NMR in $CDCl_3$ at room temperature showed signals at $\delta = -0.55$ (d, $^2J_{P-P} = 33.4$ Hz); 58.96 (s); 64.5 (d, $^2J_{P-P} = 33.4$ Hz). MS (ESI+) experiments showed the presence of an ion at $m/z = 925$ (100%, other signals under 10%), for which the isotopic pattern matches that of ([Ru(**1**)$_2$(acac)]$^+$; see Supporting Information). These data are interpreted as **5a**/**5b** being two isomers and compound **5a** (signal at $\delta = 58.96$) being a *cis*-bis-phosphine complex analogous to complexes **3** and **4**. Complex **5b** (signals at $\delta = -0.55$ (d, $^2J_{P-P} = 33.4$ Hz);[13] 64.5 (d, $^2J_{P-P} = 33.4$ Hz)) has one aminopyridine ligand coordinated as a bidentate P,N-ligand, similar to the coordination mode described for 2-diphenylphosphinopyridine.[5,14] This mixture of **5a** and **5b** was used as a catalyst without further purification.

Subsequently, the new ruthenium complexes **3**−**5** were evaluated as catalysts in the hydration of 4-methylbenzonitrile (**6**). The mixture of the substrate **6**, water (2 equiv), and the catalysts **3**−**5** (1 mol %) was heated in 1,2-dimethoxyethane (DME) at 150 °C for the given time. After cooling to room temperature the reaction mixture was analyzed with ^{1}H NMR spectroscopy. The results of the kinetic measurements are depicted in Figure 5.

The highest activity was observed for the isoquinolone complex **3** (100% conversion after 20 h, maxTOF = 20 (mol amide)/(mol catalyst)·h^{-1}), the heterocomplex **4** was less active (90% conversion, maxTOF = 5 h^{-1}), and a very low activity (conversion <5%) was detected for complex **5**.

The apparent differences in the activity of the studied catalysts could stem from several facts. First, in accordance with the mechanism postulated by Oshiki (Scheme 1) the nitrile is activated upon coordination to a vacant site of the ruthenium. Ligand **2** is a weaker donor than ligand **1** due to the electron-withdrawing character of the isoquinolone substituent. Hence, the ruthenium complex of **2** should be a stronger Lewis acid compared to the complex bearing ligand **1** and could more effectively catalyze the hydrolysis of the coordinated nitrile. This electronic factor may be responsible for the observed catalyst activity **3** > **4** > **5**. Second, the nucleophilic attack of water may be facilitated by hydrogen bonding with the ligands. Two plausible scenarios for catalysts **3** and **4** respectively are depicted in Figure 6. At this stage of the project, the relative importance of this effect is difficult to quantify. As a third factor influencing catalysts activity, the pyridine nitrogen of ligand **1** may compete with the substrate for coordination on the metal. Thus, additional N-coordination via the pyridine nucleus may inhibit the formation of the required coordinative unsaturated ruthenium species that are needed for the activation of the nitrile. This may be responsible for the low catalytic activity of catalyst

(13) The high-field shift of the phosphorus is characteristic for the formation of *P,N*-coordinated four-membered chelate rings within this class of ligands; see for example: (a) Olmstead, M. M.; Maisonnat, A.; Farr, J. P.; Balch, A. L. *Inorg. Chem.* **1981**, *20*, 4060. (b) Schutte, R. P.; Retting, S. J.; Joshi, A. M.; James, B. R. *Inorg. Chem.* **1997**, *36*, 5809. (c) See also: ref 5.

(14) For a review on the coordination of 2-diphenylphosphinopyridine ligand, see: Zhang, Z.-Z.; Cheng, H. *Coord. Chem. Rev.* **1996**, *147*, 1.

5. Interestingly, the presence of the complementary ligand **2** prevents this type of deactivation, and complex **4** is substantially more active.

Conclusion

In summary, novel bis-phosphine ruthenium complexes with the isoquinolone−aminopyridine self-assembling ligand system have been prepared. Selective formation of the heterocomplex **4** was observed when a 1:1 mixture of complementary ligands was used. Two of these complexes proved to be active catalysts for the hydration of 4-methylbenzonitrile. Although at this stage the origin of the catalytic activity remains unknown, the hydrogen-bonding network may play an important role. Application of our isoquinolone−aminopyridine ligand libraries[8] in order to optimize the catalyst in a combinatorial fashion is anticipated.

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Note Added after ASAP Publication. In the version of this paper published on the Web on March 23, 2007, Scheme 1 contained some extra lines around the structures, due to a production error. The version of Scheme 1 that now appears is correct.

Supporting Information Available: Procedures for the preparation of catalysts and evaluation of the catalytic activity, characterization data, and crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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