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Synthesis of New Ruthenium-CAP Complexes and Use as Catalysts for Benzonitrile Hydration to Benzamide

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Dedicated to Prof. Rinaldo Poli, in celebration of his 65th birthday and outstanding contribution to chemistry and catalysis.

The new bimetallic $[Ru_2(\mu\text{-}Cl)_3(CAP)_6]Cl$ (**1**) and monometallic *cis*,*cis*,*trans*-$[RuCl_2(dmso\text{-}S)_2(CAP)_2]$ (**2**) complexes, bearing the water soluble cage-like phosphine CAP (1,4,7-triaza-9-phosphatricyclo[5.3.2.1]tridecane), were synthesized and characterized in solution by NMR spectroscopy and ESI-MS spectrometry. The complexes, endowed with high solubility and stability in water, were applied as catalysts for the proof-of-concept hydration of benzonitrile to benzamide in neat water at 100 °C, achieving high conversions with only 1 mol% of catalyst, both in single runs and in catalyst recycling experiments.

Introduction

The coordination chemistry of ruthenium(II) has received in the last century wide attention, involving the use of large libraries of ancillary ligands based on elements such as phosphorus, nitrogen, sulfur, oxygen and many more. Among the various applications of Ru complexes, a well represented field of research is homogeneous catalysis, in particular for the synthesis of fine chemicals and pharmaceutical intermediates.[1] Successful examples of Ru-catalyzed processes include among others hydrogenation and transfer hydrogenation,[2] olefin metathesis,[3] ring-opening[4] and ring-closing reactions,[5] alkyne and nitrile hydration.[6,7]

In order to avoid the use of large amounts of toxic solvents and the formation of waste by-products in catalytic reactions, many research groups have designed water-soluble ligands and obtained the corresponding metal complexes for use in water-phase or biphasic water-organic solvent processes.[8] Among neutral water soluble phosphines, the cage-like bifunctional ligand 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane (PTA) and its derivatives have found large use in catalysis, as well as in materials science and medicinal chemistry.[9] Ru-PTA coordination chemistry has been largely developed, in particular that of half-sandwich Ru(II)-arene and cyclopentadienyl complexes, for their use in catalysis[10,11] and medicinal chemistry.[12] Among octahedral Ru-PTA complexes, $[Ru(PTA)_4Cl_2]$, a well-studied complex with peculiar isomerism properties, found use as catalyst in several reactions in aqueous or biphasic media, including hydrogenation of aldehydes,[13a] olefins,[13b] carbon dioxide,[14] and more recently hydration of nitriles to amides.[15] Amide synthesis by metal-catalyzed organonitrile hydration[16] can bring several advantages over traditional protocols based on the use of carboxylic acids with amines and strong acids or bases,[17] as it can allow milder reaction conditions, wide functional group compatibility, high atom efficiency and high selectivities by minimizing the formation of kinetically favoured carboxylic acids.

Examples of Ru catalysts for nitrile hydration to amides in neat water[18] include $[Ru(\eta^6\text{-arene})Cl_2(PR_3)]$ (η^6-arene = C_6H_6, p-cymene, C_6Me_6; R = NMe_2, OMe, OEt, Et, iPr),[19a] $[Ru(\eta^6\text{-arene})Cl_2(PR_2R')]$ [PR_2R' = $PMe_2(CH_2P(O)Me_2)$, $PMe_2(CH_2CH_2P(O)Me_2)$, $PPh_2(CH_2P(O)Ph_2)$, $PPh_2(CH_2CH_2P(O)Ph_2)$, PMe_2OH, $P(OEt)_2OH$],[19b] $[RuCl_2(\eta^6\text{-arene})(PR_2OH)]$ and $[RuCl_2(\eta^6\text{-arene})\{P(OR)_2OH\}]$ (R = Me, Ph; η^6-arene = C_6H_6, p-cymene, 1,3,5-$C_6H_3Me_3$, C_6Me_6)[20] and other bifunctional catalysts,[21] also in combination with PTA such as in the recent case of $[RuCl(\eta^6\text{-arene})(PFu_3)(PTA)]BF_4$ (PFu_3 = tris(2-furyl)phosphine).[22] Lower-rim PTA derivatives such as 1-benzyl-3,5-diaza-1-azonia-7-phosphaadamantane chloride (PTA–Bn), were used to obtain Ru catalysts, for example the well-defined complex $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{–}Bn)]$,[23] and the system obtained *in situ* by combination of PTA–Bn with $[RuCl_2(dmso)_4]$ (dmso = dimethylsulfoxide) in 3:1 ratio, that were both used for hydration of various nitriles.[24] Complexes bearing some upper-rim PTA derivatives such as $[RuCl(\eta^6\text{-toluene})\{\kappa^2\text{-PTA–C(NHPh)}Ph_2\}]Cl$ and $[RuCl_2(\eta^6\text{-toluene})(PTA\text{-}P^iPr_2)]$ [PTA-P^iPr_2 = 6-(diisopropylphosphino)-1,3,5-triaza-7-phosphaadamantane] were also tested for this reaction.[25] Drawings of PTA and its derivatives that found use in Ru-catalyzed nitrile hydration are sketched in Figure 1.

Recently, Britvin and coworkers reported the synthesis of the new cage-like water soluble phosphine 1,4,7-triaza-9-phosphatricyclo[5.3.2.1]tridecane, to which they gave the acronym of CAP (Figure 1).[26] Although examples of CAP complexes of Au,[26a] Pt and Pd,[27,28] Tc and Re,[29] and Rh[30] were reported, its coordination chemistry with Ru is still underdeveloped. We recently reported the synthesis of the Ru-arene CAP complexes $[RuCl_2(\eta^6\text{-}p\text{-cymene})(CAP)]$ (RACAP–C) and $[RuCl(\eta^6\text{-}p\text{-cymene})(L)(CAP)]PF_6$ (L = CAP or MeCN), that showed to be

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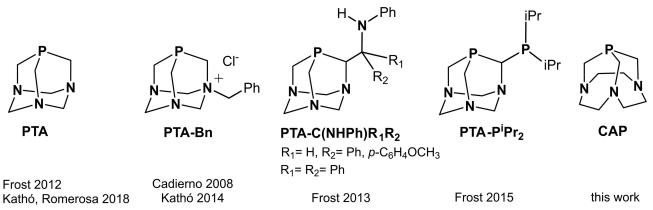


Figure 1. Water-soluble cage-like phosphines used in Ru-catalyzed nitrile hydration.

active *in vitro* anticancer agents.[31] In catalytic applications, they showed higher activity than the corresponding PTA analogues in the transfer hydrogenation of C=N bonds using sodium formate as reducing agent in water under mild temperature conditions (80 °C).[32] The chemical reactivity of CAP in comparison with that of PTA and CAP metal complexes reported so far have been recently reviewed.[33]

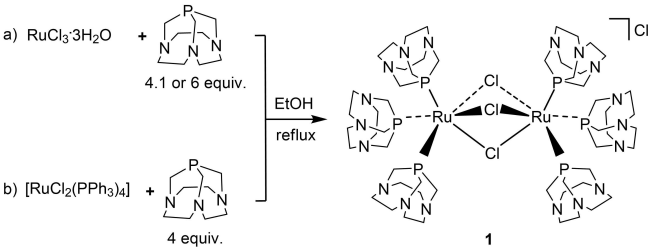
In order to further explore the coordination ability of CAP to Ru, we planned to synthesize novel octahedral arene-free complexes and to test them as proof-of-concept catalysts for benzonitrile hydration to benzamide in neat water, comparing the results to those obtained with PTA analogues. The main results, including catalyst recycling experiments, are hereby described.

Results and Discussion

Synthesis of the new octahedral Ru-CAP compounds

Inspired by literature reports, we initially explored the possibility to obtain the CAP analogue of $[RuCl_2(PTA)_4]$, following the synthetic procedure described by Darensbourg, Joó and coworkers,[13a] replacing PTA with CAP. Thus, $RuCl_3 \cdot 3H_2O$ was reacted with 6 equiv. of CAP in 96% EtOH under reflux conditions and after 5 h the formation of a precipitate was observed. Both the solid and the yellow solution were analysed by $^{31}P\{^1H\}$ NMR in $CDCl_3$ showing a main singlet at 85.01 ppm, together with a small signal due to the residual free CAP (47.80 ppm) and two unidentified broad peaks at 89.16 and 52.59 ppm, respectively. To minimize by-product formation and ensure the use of all CAP as ligand for the metal, the reaction was repeated using a smaller excess of phosphine (4.1 equiv.) under reflux conditions for 24 h. After workup, a yellow solid was collected in air, dried under vacuum and characterized in solution by NMR spectroscopy. The $^{31}P\{^1H\}$ NMR spectrum in $CDCl_3$ showed only the previously observed singlet at 85.01 ppm, slightly shifted to 87.01 ppm in D_2O. The large low field shift of the ^{31}P NMR resonance from 47.80 ppm (free CAP) to 85.01 ppm confirms the expected coordination of CAP to the metal. The ^1H NMR spectrum of the new complex in $CDCl_3$ consists of three signals, namely a broad singlet at 3.58 ppm for PCH_2N and two multiplets in the range 3.13–3.05 ppm and 2.93–2.90 ppm due to the $N(CH_2)_2N$ methylene groups, all with the same integral value. Since our efforts to grow single crystals suitable for X-ray diffraction were not successful, we turned to electron spray ionization mass spectrometry (ESI-MS) as an additional tool to establish the formula of the new complex and the number of CAP ligands coordinated to the ruthenium centre. The ESI-MS spectrum of a sample of the compound dissolved in $CHCl_3$ and diluted with MeOH up to a concentration of 20 ng/μL showed a peak at *m/z* 1503.4 (100) belonging to $[M–Cl]^+$, a value consistent with the formula $[Ru_2Cl_3(CAP)_6]^+$. This is reminiscent of the related bimetallic PTA compound $[Ru_2(\mu\text{-}Cl)_3(PTA)_6]Cl$, which was reported to form by reaction of PTA with $RuCl_3 \cdot 3H_2O$ or other ruthenium precursors such as *cis*-$[RuCl_2(dmso)_2(PTA)_2]$ under various conditions.[34] The formation of stable, symmetrically chloro-bridged homobimetallic Ru complexes is well documented in the literature. As early as in 1961, Chatt and Hayter reported that reactions of $RuCl_3$ with tertiary phosphines such as PMe_2Ph, PEt_2Ph, $PMePh_2$ or $PEtPh_2$ in alcohols under reflux conditions gave complexes of the type $[Ru_2(\mu\text{-}Cl)_3(PR_3)_6]Cl$.[35] Other trichloro-bridged phosphine diruthenium complexes have been isolated and characterized in the solid state,[36] and recently, compounds such as $[Ru_2(\mu\text{-}Cl)_3(PR_3)_6]Cl$ were used as precursors for the synthesis of $[Ru_2(OTf_3)_3(PR_3)_6](OTf)$ (OTf = SO_2CF_3; PR_3 = $PEt_2(p\text{-}Me_2N–Ph)$, $PMePh_2$, PEt_3), that were used as catalysts for the selective oxidation of polyol natural products to the corresponding ketones.[37] The simulated mass spectrum of a complex with formula $[Ru_2Cl_3(CAP)_6]^+$ matches well the experimental data, featuring the typical isotopic pattern due to ruthenium and chlorine (see Figures S5–S9 in Supporting Information). Based on the experimental findings and the data reported in the literature, we assign the formula $[Ru_2(\mu\text{-}Cl)_3(CAP)_6]Cl$ (**1**) to the newly synthesized complex. Complex **1** is highly stable and could be stored under air as solid, without any sign of decomposition for prolonged time. It shows good solubility in water, with a measured value of $S(H_2O)_{20°C} = 1.25$ g/L, and proved to be remarkably stable in this solvent. $^{31}P\{^1H\}$ NMR spectra run at different times showed that solutions of **1** in water remained unchanged even after more than 8 days under air and exposure to sunlight.

The effects of different reaction conditions and type of metal precursor on the synthesis of **1** were then briefly assessed (Scheme 1). The complex was obtained starting from $RuCl_3 \cdot 3H_2O$ (path a), with either 4.1 or 6 equiv. of CAP. On the other hand, yields lower than 20% (based on ^{31}P NMR analysis) were observed using the same precursor with only 3 equiv. of ligand. $[RuCl_2(PPh_3)_4]$ was also tested as alternative metal



Scheme 1. Synthetic pathways to $[Ru_2(\mu\text{-}Cl)_3(CAP)_6]Cl$ (**1**).

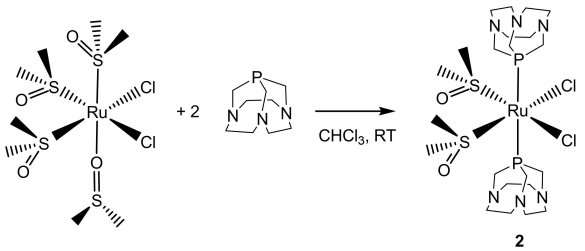
precursor by reaction with 4 equiv. of CAP under the same conditions (path b), but in this case the $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture showed, together with **1** and free PPh_3, the formation of several unknown by-products, that would require tedious purification steps. $RuCl_3 \cdot 3H_2O$ was thus confirmed as the most suitable synthetic precursor for **1**.

We then tested the possibility to use **1** as a precursor for the synthesis of monometallic complexes, by chloride bridge cleavage. At first, **1** was reacted with $TlPF_6$ in the presence of an excess of CAP (6.5 equiv.) in toluene/ethanol (1:1) mixture under reflux conditions for 24 h. As $^{31}P\{^1H\}$ NMR analysis showed again the original signal at 85.01 ppm, we conclude that no Cl bridge cleavage occurred. Next, **1** was dissolved in acetonitrile in the presence of $AgPF_6$ (4.15 equiv.) and left under reflux conditions. In this case, only partial decomposition was observed. Finally, the addition of CAP (2.2 equiv.) to **1** in aqueous solution under reflux for 24 h did not bring about bridge cleavage, as only the signals due to **1** and free CAP were observed in the $^{31}P\{^1H\}$NMR spectrum of the crude mixture at the end of the test. These observations suggest a high chemical and thermal stability of **1** and that, in contrast to the reactivity shown with PTA, the synthetic routes described above cannot be used to obtain the CAP analogue of $[RuCl_2(PTA)_4]$.

Next, we decided to test *cis*,*fac*-$[RuCl_2$(dmso-*O*)(dmso-*S*)$_3]$,[38,39] a well-known Ru(II) precursor, for the synthesis of Ru-CAP complexes. This precursor is more versatile than $RuCl_3$ to obtain well-defined Ru(II) derivatives, as it does not require prior Ru(III) to Ru(II) reduction and dmso may be displaced by strongly coordinating ligands such as phosphines, phosphites and dithiocarbamates,[38] pyrazolylpyridines[40] and azoles.[41] Kathó and coworkers indeed reported the synthesis of *cis*,*cis*,*trans*-$[RuCl_2$(dmso-*S*)$_2$(PTA)$_2]$ starting from this precursor.[42] Interestingly, both this compound and other Ru(II)-dmso complexes[40,41] have been applied as catalysts for nitrile hydration with good results. Using the literature reaction conditions, *i.e.* reacting the Ru precursor with two equivalents of CAP in $CHCl_3$ at room temperature (Scheme 2) in analogy with the PTA counterpart, we obtained as expected the new octahedral ruthenium(II) complex *cis*,*cis*,*trans*-$[RuCl_2$(dmso-*S*)$_2$(CAP)$_2]$ (**2**). The product, isolated as a light yellow solid in 63% yield, was characterized in solution by NMR and ESI-MS techniques. In the ^1H NMR spectrum of **2**, the two CH_3 groups of coordinated dmso were identified as a singlet at 3.43 ppm, a chemical shift value in line with that of the corresponding PTA derivative (3.35 ppm in $CDCl_3$).[42] The ratio of integrals of the ^1H NMR signals of coordinated dmso and the CH_2 signals of CAP confirms the proposed formula. The mutual *trans* position of the two CAP ligands was confirmed by the presence of a unique singlet at 40.92 ppm in the corresponding $^{31}P\{^1H\}$ NMR spectrum. In the $^{13}C\{^1H\}$ NMR spectrum ($CDCl_3$), the two *cis*-coordinated dmso ligands showed a singlet at 52.55 ppm, a value similar to that reported for *cis*,*cis*,*trans*-$[RuCl_2$(dmso-*S*)$_2$(PTA)$_2]$ (51.18 ppm in $CDCl_3$).[42] Finally, a hetero-correlated ^1H-^{13}C HSQC (*Heteronuclear Single Quantum Coherence*) 2D-NMR experiment was carried out for the attribution of the ^{13}C signals of the phosphine cage in **2** (Figure S12, Supporting Information). Two singlets were observed, one at 51.12 ppm for the methylene carbon atoms of the triazacyclononane ring and one at 49.77 ppm due to PCH_2N carbons, at values comparable with those observed for **1** (Figure S11 and Experimental Section). The ESI-MS analysis also confirmed the formula of **2**, featuring a peak at *m/z* 613.0 (100), corresponding to the cationic species $[RuCl(dmso\text{-}S)(CAP)_2]^+$, formed upon loss of one dmso and one chloride ligands. The solubility in water of **2** is $S(H_2O)_{20°C} =$ 20.0 g/L, more than an order of magnitude higher than **1**. Complex **2** resulted to be stable in water, as neither signals of free dmso nor of CAP were detected in ^1H NMR spectra of a sample of **2** in D_2O, checked after 24 h and 48 h.

Alessio and coworkers showed that *cis*,*cis*,*trans*-$[RuCl_2$(dmso-*S*)$_2$(PTA)$_2]$ can be further used as precursor of other Ru-PTA derivatives by replacement of dmso with chelating diimines, such as 2,2′-bipyridine (bpy) or 2,2′-bipyridine-4-carboxylic acid (bpyAc).[43] Thus, we tested **2** as precursor for monometallic Ru-CAP complexes at higher CAP:Ru ratios. At first, **2** was reacted with 2 equiv. of CAP in $CHCl_3$ for 2 h at room temperature, but no reactivity was observed. Next, the temperature was increased to reflux conditions and the reaction was left running for 2 h. The $^{31}P\{^1H\}$ NMR spectrum of the crude mixture showed two singlets, one due to free CAP and the other at 85.5 ppm, a chemical shift value very close to that previously observed for **1**. Finally, the reaction was repeated in CH_2Cl_2 at room temperature, and after 24 h the $^{31}P\{^1H\}$ NMR spectrum showed the presence of various peaks in the range 89.1–52.6 ppm, including unreacted CAP and **2**, suggesting that this method does not lead to any well-defined products.

In conclusion, the known methods described in the literature to obtain $[RuCl_2(PTA)_4]$ did not lead to the CAP analogue $[RuCl_2(CAP)_4]$. This may be related to the unusual steric and electronic properties of CAP, and to the behaviour of the bimetallic complex **1** as a thermodynamic sink in these reactions.



Scheme 2. Synthesis of *cis*,*cis*,*trans*-$[RuCl_2$(dmso-*S*)$_2$(CAP)$_2]$ (**2**).

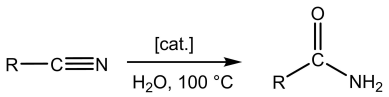
Catalytic nitrile hydration

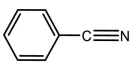
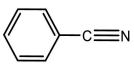
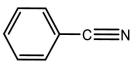
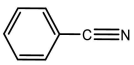
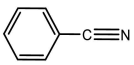
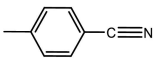
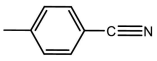
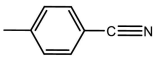
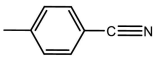
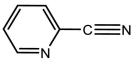
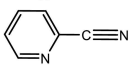
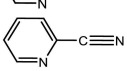
As complexes *cis*,*cis*,*trans*-$[RuCl_2$(dmso-*S*)$_2$(PTA)$_2]$ and $[Ru_2(\mu\text{-}Cl)_3(PTA)_6]Cl$ were shown to be active catalysts for the hydration of nitriles to amides,[24a,34] we decided to test **1** and **2** in the proof-of-concept benzonitrile hydration to benzamide under the reaction conditions applied in the literature,[15a] *i.e.* 1 mmol of substrate in 3 mL of neat water at 100 °C, but reducing the catalyst amount from 5 mol% to 1 mol%. Under these con-

ditions, after 7 h a conversion of only 35% was observed with **1**, while no conversion was observed with **2**. As demonstrated for the Ru-PTA systems,[24a,34] the addition of two or more equivalents of free phosphine to the reaction mixtures proved to be beneficial for the catalytic performance. The free ligand likely acts as reservoir for the complex, preventing irreversible catalyst decomposition during the catalytic runs. Thus, we applied this set of conditions in the present study, obtaining the catalytic systems **A** (**1** + 2 equiv. of CAP to dimer) and **B** (**2** + 2 equiv. of CAP). The results of catalytic nitrile hydration tests are summarized in Table 1. For both systems **A** and **B**, using 1 mol% of catalyst, fully selective and almost quantitative conversions of benzonitrile to benzamide were reached after only 5 h (Table 1, entries 1 and 4), corresponding to a TON of 99.6, slightly higher than the values obtained with $[RuCl_2(PTA)_4]$ (TON = 87.0)[15a] and with systems $[Ru_2(\mu\text{-}Cl)_3(PTA)_6]Cl$ + 2 PTA (TON = 19.8) and *cis*,*cis*,*trans*-$[RuCl_2(dmso)_2(PTA)_2]$ + 2 PTA (TON = 15.8).[34] Control tests showed that $[RuCl_2(dmso)_4]$ alone is not active for nitrile hydration.[24] The homogeneous nature of our catalytic systems was confirmed by standard Hg(0) poisoning test, a largely used method to rule out the contribution to catalysis by heterogeneous metal particles that may form under reaction conditions. By repeating the catalytic run described in Table 1 entry 4, in the presence of an excess of metallic mercury, no evident effect was observed on benzonitrile conversion, that reached 96% after 5 h.

Next, the substrate concentration was raised to 0.83 M, leading to a substrate to catalyst ratio of 250. After 8 h, system **A** gave 89% conversion corresponding to a TON of 222.0 (Table 1, entry 2), while system **B** achieved 99% conversion with TON = 248.7 (Table 1, entry 5). Finally, after raising the benzonitrile concentration to 1.67 M, corresponding to a substrate to catalyst ratio of 500, system **A** resulted still active reaching *ca.* a 18% conversion after 6 h at 100 °C (Table 1, entry 3). The test was left running for 24 h, observing a final substrate conversion of *ca.* 48%. However, partial catalyst decomposition probably occurred at this longer reaction time, as indicated by a slight darkening of the solution and by the appearance of additional unknown signals in the $^{31}P\{^1H\}$ NMR spectrum of an aliquot of the reaction mixture analyzed at the end of the test. Importantly, in all tests described, the hydration of benzonitrile to benzamide was fully selective, as no traces of benzoic acid or other by-products were observed in the corresponding gas-chromatograms of reaction mixtures (retention time values based on pure samples: benzonitrile 9.67 min; benzamide

Table 1. Catalytic nitrile hydration to amides in the presence of systems **A** and **B**[a]



Entry	Catalytic System	Substrate	Sub/cat	[sub] [M]	Conv [%][c]	Time [h]	TON[d]
1	**A**		100	0.33	99	5	99.6
2	**A**		250	0.83	89	8	222.0
3	**A**		500	1.67	18	6	89.5
4	**B**		100	0.33	99	5	99.5
5	**B**		250	0.83	99	8	248.7
6	**A**		100	0.33	83	8	82.8
7	**A**		250	0.83	44	8	110.2
8	**B**		100	0.33	83	8	82.9
9	**B**		250	0.83	56	8	139.0
10	**A**		100	0.33	27	8	26.7
11	**A**		20	0.07	67	8	13.5
12	**A**[b]		20	0.20	89	8	17.9

[a] General conditions: substrate, catalytic system **A** (**1**, 0.01 mmol + CAP, 0.02 mmol) or **B** (**2**, 0.01 mmol + CAP, 0.02 mmol), H_2O (3 mL), 100 °C. [b] Conditions: substrate (0.2 mmol), catalytic system **A** (**1**, 0.01 mmol + CAP, 0.02 mmol), H_2O (1 mL), 100 °C. [c] Substrate conversions (%) determined by GC analysis (uncorrected areas). [d] TON = (mmol product)/(mmol catalyst).

17.57 min; benzoic acid 15.95 min, see Figure S16 in Supporting Information).

Encouraged by the good results obtained with benzonitrile, we decided to test a few selected, highly water-soluble aryl nitriles as substrates. In the case of *p*-tolunitrile, comparable conversions to benzonitrile (83%) were observed with both systems **A** and **B** after 8 h using 1 mol% of catalyst (Table 1, entries 6 and 8). In contrast, when the test was performed using a substrate to catalyst ratio of 250, system **B** showed a better performance than system **A** (56% *vs.* 44% conversion, entries 7 and 9). In the case of *o*-tolunitrile, no conversion was observed, regardless of type and amount of catalyst. This is in line with literature data, showing that *ortho*-substituted benzonitriles exhibit low conversions to the corresponding amides probably due to steric factors, hampering substrate coordination to the metal.[44,45] Then, 2-pyridinecarbonitrile was chosen as substrate. This is a rather difficult substrate for catalytic hydration, as previously described with different Ru-PTA systems. For instance, using 5 mol% of the catalyst formed *in situ* from $[RuCl_2(dmso)_4]+3$(PTA–Bn), only 10% conversion to 2-pyridinecarboxamide was obtained after 1 h.[24a] In the case of $[RuCl_2(PTA)_4]$[15a] and $[RuCl_2(\eta^6\text{-toluene})(PTA\text{-}P^iPr_2)]$,[25b] conversions of 43% and 36% were obtained after 7 h at 100 °C, respectively, using 5 mol% of catalyst. Using system **A** at a substrate concentration of 0.33 M and a substrate to catalyst ratio of 100, 27% conversion to 2-pyridinecarboxamide was obtained after 8 h (Table 1, entry 10). Catalytic system **A** reached 67% conversion after 8 h with a substrate concentration of 0.07 M (Table 1, entry 11), and up to 89% with a substrate concentration of 0.20 M (Table 1, entry 12). In contrast, system **B** was not active in 2-pyridinecarbonitrile hydration under the same reaction conditions. As for benzonitrile, complete selectivities to amides were observed also with these substrates, as no by-products were detected by GC analyses of the reaction mixtures.

Finally, proof-of-concept catalyst recycling experiments were carried out using benzonitrile as substrate and system **A** as catalyst (Figure 2). All consecutive runs were performed under the standard conditions described above, *i.e.* using 1 mol% of catalytic system **A**, 3 mL of water, 100 °C. After 6 h, substrate conversion was determined for each run taking an aliquot of the solution and analyzing it by GC. The catalytic mixture was then cooled overnight to favour amide precipitation. The next day, the clear yellow aqueous solution containing the catalytic system was transferred to a new reactor, to which a new batch of fresh benzonitrile (1 mmol) was added. The mixture was then heated to 100 °C and the following run was started. The first five recycling runs gave quite similar conversions, in the range 99–97%, which is indicative of good stability and constant activity of the catalytic system. From run VI, a decrease in conversion was observed. This effect may be due to the progressive depletion of catalyst from the transferred water phase and sampling for GC analysis as suggested by other authors.[15a,46]

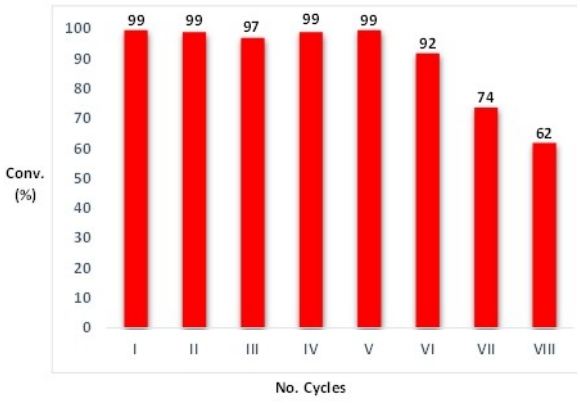


Figure 2. Conversions (%) in catalyst recycling tests for benzonitrile hydration to benzamide in the presence of system **A** in neat water, 100 °C.

Conclusion

Two new octahedral ruthenium(II) complexes bearing the water-soluble cage-like aminophosphine ligand CAP, namely the bimetallic $[Ru_2(\mu\text{-}Cl)_3(CAP)_6]Cl$ (**1**) and monometallic *cis*,*cis*,-*trans*-$[RuCl_2(dmso\text{-}S)_2(CAP)_2]$ (**2**), were synthesized starting from readily available ruthenium precursors and isolated in good yields. Both complexes showed high stability and good solubility in water and, in the presence of free CAP as the only additive, behave as efficient catalysts in the proof-of-concept selective hydration of benzonitrile and selected aryl nitriles in neat water, with high conversions and selectivity to the corresponding amides. Compared to PTA, the CAP-based ruthenium catalysts required shorter reaction times, and were efficient at higher substrate concentrations. In addition, the catalytic system **A** obtained from complex **1** + free CAP resulted to be active in the preliminary test of 2-pyridinecarbonitrile hydration, a substrate for which low conversions were described with different Ru-PTA systems. Catalyst recycling experiments, based on simple reuse of the water phase after filtration of the organic product without further workup, showed that system **A** was able to convert almost quantitatively benzonitrile to benzamide, for five consecutive runs without significant loss of activity.

Experimental Section

General materials and methods

All manipulations were carried out under a purified N_2 atmosphere using standard Schlenk techniques unless otherwise noted. Deuterated solvents and other reagents were bought from commercial suppliers and used without further purification. Doubly distilled water was used and dichloromethane was distilled, dried and degassed prior to use. The phosphine CAP[26a,31] and the ruthenium precursor *cis*,*fac*-$[RuCl_2(dmso\text{-}O)(dmso\text{-}S)_3]$[38] were synthesized as reported in the literature and the latter was kept and used in the dark due to its sensitivity to light. ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$ NMR and ^1H-^{13}C HSQC (Heteronuclear Single Quantum Coherence) NMR spectra were recorded on a Bruker Avance II spectrometer (operating at 400.13, 100.61 and 161.98 MHz, respectively) or a Bruker DRX 300

spectrometer (operating at 300.13, 75.47 and 121.50 MHz, respectively). The ^{13}C and ^{31}P NMR spectra were normally run with proton decoupling. ^{31}P NMR spectra are reported in ppm relative to an external H_3PO_4 standard (0.0 ppm), with downfield positive shifts. $^{13}C\{^1H\}$ NMR spectra are reported in ppm relative to residual solvent resonances with downfield positive shifts. ESI-MS spectra were done on a LCQ Orbitrap mass spectrometer (ThermoFischer, San Jose, CA, USA) equipped with a conventional ESI source by direct injection of the sample solution and are reported in the form *m/z* (intensity relative to base = 100). Elemental analyses were carried out by a Perkin-Elmer 2400 series II elemental analyzer. GC-analyses were performed on a Shimadzu GC 2010 Plus gas chromatograph equipped with flame ionization detector and a SPB™-1 capillary column (30 m, 0.25 mm ID, 0.25 μm film thickness). GC–MS analyses were performed on a Shimadzu QP2010S apparatus equipped with a flame ionization detector and a Supelco SPB1 fused silica capillary column (30 m, 0.25 mm ID, 0.25 μm film thickness). The solubility of compounds in water was assessed by adding bidistilled H_2O with a 500 μL Hamilton microsyringe to a 3 mg sample of the compound placed in a Schlenk flask, under slow stirring in a thermostated bath kept at 20 °C, until complete dissolution of the solid.

Syntheses of Ruthenium Complexes

Synthesis of $[Ru_2(\mu\text{-}Cl)_3(CAP)_6]Cl$ (1). In a Schlenk flask, $RuCl_3\cdot 3H_2O$ (0.05 g, 0.19 mmol) and CAP (0.156 g, 0.78 mmol) were dissolved in 96% EtOH (31 mL) and refluxed under a nitrogen atmosphere for 24 h. During this time the colour of the reaction mixture changed from dark brown reddish to light green yellowish. The solvent was then removed under reduced pressure yielding a green powder. This was redissolved in dichloromethane (30 mL) and the mixture was filtered by cannula to remove the insoluble residue. Then, diethylether (50 mL) was added to the clear solution giving a yellow precipitate which was collected in air and dried under vacuum (0.13 g, 88.9% yield). $S(H_2O)_{20°C} = 1.25$ g/L. ^1H NMR (400.13 MHz, $CDCl_3$): δ (ppm) 3.58 (br s, 36H, PCH_2N); 3.13–3.05 (m, 36H, $N(CH_2)_2N$); 2.93–2.90 (m, 36H, $N(CH_2)_2N$). $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ (ppm) 54.81 (s, PCH_2N); 51.17 (s, $N(CH_2)_2N$). $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$): δ (ppm) 85.01 (s, 6P, CAP). ^1H NMR (300.13 MHz, D_2O): δ (ppm) 3.52 (br s, 36H, PCH_2N); 3.15–3.10 (m, 36H, $N(CH_2)_2N$); 2.86–2.83 (m, 36H, $N(CH_2)_2N$).$^{31}P\{^1H\}$ NMR (121.50 MHz, D_2O): δ (ppm) 87.01 (s, 6P, CAP). MS (nESI+; m/z) $[Ru_2(\mu\text{-}Cl)_3(CAP)_6]^+$: 1503.4 (100) $[M]^+$; 752.8 (79) $[M+H]^{2+}$. Anal. found (calcd. for $C_{54}H_{108}Cl_4N_{18}P_6Ru_2$, 1539.35 $gmol^{-1}$): C, 42.19 (42.13); H, 7.10 (7.07); N, 16.29 (16.38).

Synthesis of *cis,cis,trans*-$[RuCl_2(dmso\text{-}S)_2(CAP)_2]$ (2). Under an inert atmosphere of nitrogen, a Schlenk tube was charged with *cis,fac*-$[RuCl_2(dmso\text{-}O)(dmso\text{-}S)_3]$ (0.06 g, 0.12 mmol) and CAP (0.05 g, 0.25 mmol). Dry and degassed dichloromethane (10 mL) was added by syringe and the resulting yellow solution was left stirring in the dark at room temperature. After 2.5 h, the volume of the solution was reduced under vacuum to *ca.* 4 mL and 10 mL of cold diethylether were added under stirring. The resulting precipitate was left to deposit on the bottom of the tube and the solution was removed by syringe. The yellow solid was washed with cold diethylether (1 mL × 2) and dried under reduced pressure (0.55 g, 63.1% yield). $S(H_2O)_{20°C} = 20.0$ g/L. ^1H NMR (400.13 MHz, $CDCl_3$): δ (ppm) 3.88 (t, $J_{HP} = 3.8$ Hz, 12H, PCH_2N); 3.43 (s, 12H, dmso-CH_3); 3.04–2.90 (m, 24H, $N(CH_2)_2N$). $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ (ppm) 52.55 (s, dmso-CH_3); 51.12 (s, $N(CH_2)_2N$); 49.77 (s, PCH_2N). $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$): δ (ppm) 40.92 (s, 2P, CAP). MS (nESI+; m/z): 613.0 (100) $[Ru(dmso)Cl(CAP)_2]^+$. Anal. found (calcd. for $C_{22}H_{48}Cl_2N_6O_2P_2RuS_2$, 726.71 $gmol^{-1}$): C, 36.22 (36.36); H, 6.86 (6.66); N, 11.50 (11.56).

General procedure for catalytic nitrile hydration

All reactions were carried out in a Schlenk tube under an inert atmosphere of nitrogen. In a typical experiment, the catalyst (0.01 mmol) and the ligand CAP (4 mg, 0.02 mmol) were dissolved in water (3 mL) and the resulting clear solution was put into an oil bath heated to 100 °C. Once the temperature was reached, nitrile was added and the catalytic reaction was left stirring at 100 °C for the desired time. At the end of the catalytic run, a small aliquot of the reaction mixture (0.1 mL) was taken by syringe, diluted with ethanol (0.4 mL) and analysed by GC (two consecutive injections for each aliquot taken). The conversion of nitrile to the corresponding amide was calculated on the basis of GC area%. The products of the hydration tests were confirmed by GC-MS analyses and ^1H NMR spectra. Each catalytic test was repeated at least twice to check for reproducibility.

Catalyst recycling tests

The recycling tests were run using benzonitrile as substrate under the standard conditions described above (**1**, 0.01 mmol; CAP, 0.02 mmol; benzonitrile, 1 mmol; water, 3 mL; 100 °C, 6 h). After the first cycle, the conversion was assessed by GC analysis of an aliquot of the reaction mixture, then the Schlenk tube was left at 4 °C overnight in order to promote the precipitation of crystals of benzamide. The following day, the aqueous solution was transferred by syringe in another Schlenk tube together with a small amount of freshly added water (*ca.* 0.3 mL) used to rinse the amide crystals from the catalytic solution adsorbed onto them. To the transferred solution, fresh benzonitrile (1 mmol) was added and the reaction was left stirring for 6 h at 100 °C for the next catalytic run.

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Conflict of Interest

The authors declare no conflict of interest.

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