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Chlorophosphines as auxiliary ligands in ruthenium-catalyzed nitrile hydration reactions: Application to the preparation of β-ketoamides

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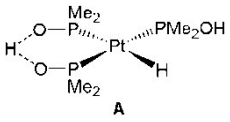
The catalytic hydration of nitriles into amides, in water under neutral conditions, has been studied using a series of arene-ruthenium(II) complexes containing commercially available chlorophosphines as auxiliary ligands, *i.e.* compounds $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PR_2Cl)]$ (R = aryl, heteroaryl or alkyl group). In the reaction medium, the coordinated chlorophosphines readily undergo hydrolysis to generate the corresponding phosphinous acids PR_2OH, which are well-known "cooperative" ligands for this catalytic transformation. Among the complexes employed, best results were obtained with $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$. Performing the catalytic reactions at 40 °C with 2 mol% of this complex, a large variety of organonitriles could be selectively converted into the corresponding primary amides in high yields and relatively short times. The application of $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ in the preparation of synthetically useful β-ketoamides is also presented.

Introduction

Hydration of nitriles (RC≡N) to the corresponding primary amides ($RC(=O)NH_2$) is a valuable reaction in academia and industry. Amides are used, not only as intermediates in organic synthesis, but also for a wide variety of applications in the production of polymers, lubricants, pharmaceuticals, herbicides, and detergents.[1] Traditional methods to hydrate nitriles involve the use of strong acids and bases as promoters.[2] However, these reactions suffer from harsh conditions, low yields and selectivity due to the over-hydrolysis of the amides into carboxylic acids, a kinetically favoured process,[3] and have a significant environmental footprint. To circumvent these problems, several catalytic processes have been devised utilizing enzymes,[4] transition metal complexes,[5] heterogeneous catalysts,[6] and metal nanoparticles.[7] In this context, among the different catalysts currently known, the Pt(II) complex $[PtH\{(PMe_2O)_2H\}(PMe_2OH)]$ (**A** in Fig. 1), developed by Parkins, is probably who has attained the greater success.[8] As a matter of fact, the remarkable activity, selectivity, and functional group compatibility of this derivative have made it the catalyst of choice to promote the hydration of C≡N bonds in a huge number of synthetic approaches to structurally complex natural products and biologically active molecules.[9] Very recently, van Leeuwen and co-workers also described the successful application of a related $[PtH\{(PR_2O)_2H\}(PR_2OH)]$ (R_2 = chiral binaphthyl unit) complex in the kinetic resolution of racemic nitriles.[10]



A

Fig 1 Structure of the platinum(II) complex $[PtH\{(PMe_2O)_2H\}(PMe_2OH)]$ (**A**).

The utility of phosphinous acid PR_2OH ligands in this catalytic transformation was further demonstrated by the group of Tyler and ours with the ruthenium derivatives **B-D** (Fig. 2).[11] In particular, complexes **B** and **C** showed a remarkable activity under unusually mild conditions (temperatures below 80 °C),[11a,c,d] being even able to hydrate challenging cyanohydrins,[11a,c] substrates for which the Parkins catalyst **A** was completely inoperative.[12]

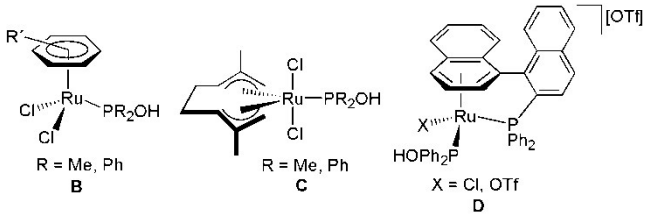


Fig 2 Structure of the ruthenium hydration catalysts **B-D**.

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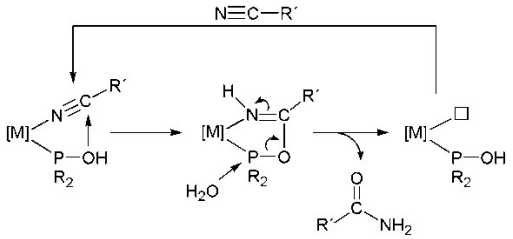
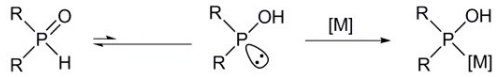
† Electronic Supplementary Information (ESI) available: Copies of the NMR spectra of complexes **2b**, **3** and **4b**, and all the amides generated in this work. CCDC 1415870 (**2g**) and 1415871 (**4c**). See DOI: 10.1039/x0xx00000x

DFT calculations performed by our group with the arene-ruthenium(II) complexes **B** unravelled the key role played by the PR_2OH ligands in these catalytic reactions. Thus, as shown in Scheme 1, the hydration process involves the initial addition of the OH group of the ligand on the coordinated nitrile, and subsequent hydrolysis of the resulting five-membered metallacycle.[11d] This reaction pathway, initially proposed without any evidence by Parkins for complex **A**,[8] contrasts with the general assumption that the metal-catalyzed hydration of nitriles must involve the direct addition of the water molecule (or the OH^- group if basic conditions are employed) on the metal-coordinated nitrile.[5]



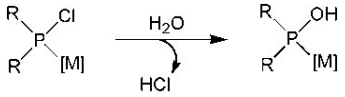
Scheme 1 The role of PR_2OH ligands in the catalytic hydration of nitriles.

On the other hand, the method most commonly employed in the literature to synthesize transition metal complexes with phosphinous acid PR_2OH ligands involves the reaction of the corresponding metallic precursor with a secondary phosphine oxide $R_2P(=O)H$.[13,14] For example, complexes **A-C** were obtained from the reactions of $[Pt(PPh_3)_4]$, $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})\}_2]$ and $[\{RuCl(\mu\text{-}Cl)(\eta^3\text{:}\eta^3\text{-}C_{10}H_{16})\}_2]$ ($C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl), respectively, with $R_2P(=O)H$ (R = Me, Ph).[8,11a,c,d] In solution, the secondary phosphine oxides exist as a tautomeric mixture of penta-, *i.e.* $R_2P(=O)H$, and trivalent, *i.e.* PR_2OH, isomers, with the pentavalent one predominating under ambient conditions.[15] In the presence of a metal this equilibrium is driven towards the PR_2OH tautomer via coordination (Scheme 2).[13]



Scheme 2 General procedure to obtain metal complexes with PR_2OH ligands.

Although comparatively much less employed, an alternative procedure to synthesize metal complexes with phosphinous acid PR_2OH ligands is by hydrolysis of coordinated chlorophosphines (Scheme 3).[16,17]

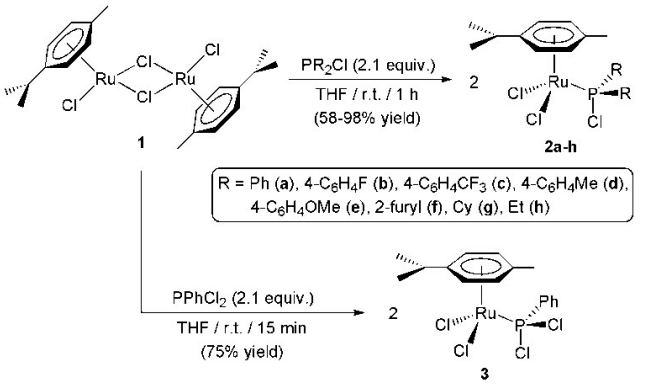


Scheme 3 Alternative procedure to generate complexes with PR_2OH ligands.

This fact opens the possibility, previously unexplored, of using chlorophosphine-metal complexes as pre-catalysts for nitrile hydration reactions, since in aqueous medium they would readily generate the cooperative PR_2OH ligands. This point would be of high practical interest because, unlike the secondary phosphine oxides, a large number of chlorophosphines are currently commercially available at relatively low prices. To confirm this possibility, we decided to synthesize, and evaluate the catalytic behaviour, of a series of ruthenium(II) complexes of general composition $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PR_2Cl)]$ (R = aryl, heteroaryl or alkyl group). As a result of this study, we present herein a new catalytic system, *i.e.* complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$, able to promote the selective hydration of nitriles to amides in pure water, at low metal loadings (2 mol%) and under mild conditions (40 °C). The application of this complex in the preparation of synthetically useful β-ketoamides, by hydration of the corresponding β-ketonitriles, is also discussed.

Results and discussion

Our research began with the preparation of a diverse family of half-sandwich $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PR_2Cl)]$ complexes **2a-h** through the treatment of the dimeric precursor $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$ (**1**) with 2.1 equivalents of different commercially available chlorophosphines (see Scheme 4). As expected, the chloride bridges cleavage reactions proceeded quickly in tetrahydrofuran at room temperature, affording complexes **2a-h** as orange-red solids in moderate to excellent yields (58-98%) after appropriate work-up (see details in the Experimental Section). Compound $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_2Cl)]$ (**2a**) was previously described in the literature.[18] Following the same approach, complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPhCl_2)]$ (**3**) could be synthesized in 75% yield from the reaction of dimer **1** with dichlorophenylphosphine (Scheme 4).



Scheme 4 Synthesis of the arene-ruthenium(II) complexes **2a-h** and **3**.

Compounds **2a-h** and **3** were characterized by means of elemental analyses and multinuclear NMR spectroscopy ($^{31}P\{^1H\}$, ^1H, $^{13}C\{^1H\}$ and $^{19}F\{^1H\}$), all data being fully consistent with the proposed formulations (details are given in the Experimental Section). In this regard, the most noticeable aspect is that, while for **2a-h** the expected deshielding of the phosphorus resonance with respect to that of the corresponding free chlorophosphine ($\Delta\delta$ = 14-38 ppm) was observed in their $^{31}P\{^1H\}$ NMR spectra, the opposite trend was found for $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPhCl_2)]$ (**3**) (δ_P = 145.6 ppm *vs* 165.0 ppm for free $PPhCl_2$). The stronger π-accepting nature of

dichloro $PRCl_2$ *vs* monochloro PR_2Cl phoshines may be behind this behaviour.[19]

In addition, the structure of complex [$RuCl_2(\eta^6$-*p*-cymene)(PCy_2Cl)] (**2g**) could be unambiguously confirmed by means of X-ray diffraction methods. X-ray quality crystals were obtained by slow diffusion of diethyl ether into a saturated solution of **2g** in dichloromethane. An ORTEP view of the molecule, along with selected structural parameters, is shown in Fig. 3. The complex features the expected three-legged "piano-stool" geometry, with the ruthenium atom surrounded by the η^6-bonded *p*-cymene ligand, two chlorides, and the phosphorus atom of PCy_2Cl. The phosphine ligand, in which both cyclohexyl groups adopt a chair conformation, is linked to ruthenium with a Ru-P1 bond length of 2.3377(8) Å, very similar to that found in the crystal structure of the related complex [$RuCl_2(\eta^6$-benzene)(PCy_2Cl)] (Ru-P = 2.3247(4) Å).[20] As observed for [$RuCl_2(\eta^6$-benzene)(PCy_2Cl)], the chlorine atom of the PCy_2Cl ligand points toward the η^6-arene to minimize the steric repulsions of the latter with the bulky cyclohexyl groups.

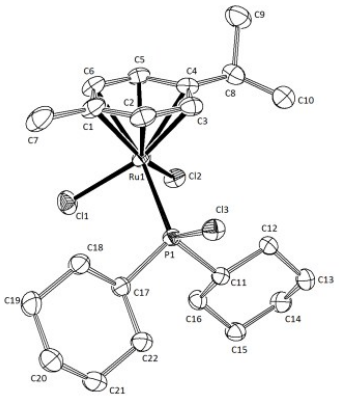
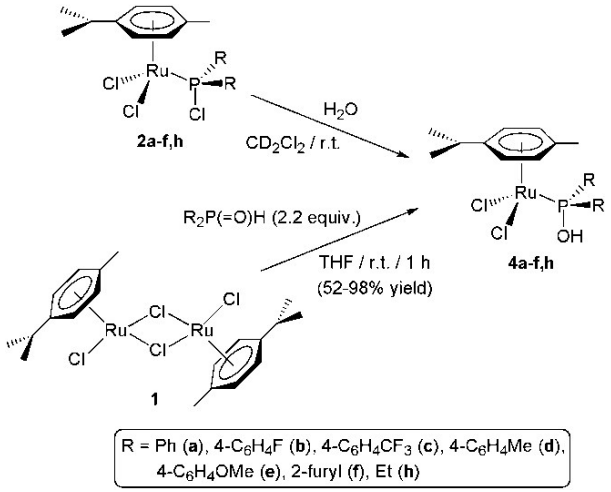


Fig 3 ORTEP-type view of the structure of complex **2g** showing the crystallographic labelling scheme. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are drawn at 30% probability level. Selected bond distances (Å): Ru-P1 2.3377(8), Ru-Cl1 2.4125(9), Ru-Cl2 2.4035(8), Ru-C* 1.7197(2), P1-Cl3 2.086(1), P1-C11 1.849(3), P1-C17 1.847(3). Selected bond angles (°): Cl1-Ru-Cl2 85.31(3), Cl1-Ru-P1 88.37(3), Cl1-Ru-C* 124.64(3), Cl2-Ru-P1 91.32(3), Cl2-Ru-C* 123.98(3), P1-Ru-C* 130.17(3), Ru-P1-Cl3 112.02(4), Ru-P1-C11 123.6(1), Ru-P1-C17 116.4(1), C11-P1-Cl3 97.5(1), C11-P1-C17 103.6(2), C17-P1-Cl3 99.8(1). C* denotes the centroid of the *p*-cymene ring (C1, C2, C3, C4, C5 and C6).

Prior to study the catalytic behaviour of complexes **2a-h** and **3**, we first explored their reactivity towards water. Experiments performed in NMR tube with CD_2Cl_2 solutions of these complexes confirmed that, upon addition of one drop of water, the chlorophosphine ligands undergo hydrolysis of the P-Cl bonds. In the case of complexes [$RuCl_2(\eta^6$-*p*-cymene)(PR_2Cl)] (R = Ph (**2a**) 4-C_6H_4F (**2b**), 4-$C_6H_4CF_3$ (**2c**), 4-C_6H_4Me (**2d**), 4-C_6H_4OMe (**2e**), 2-furyl (**2f**), Et (**2h**)) a clean transformation into the corresponding phosphinous acid derivatives [$RuCl_2(\eta^6$-*p*-cymene)(PR_2OH)] (**4a-f,h**) was observed, the hydrolysis process being faster with **2b** and **2c** containing the more electron-poor phosphines (Scheme 5). The identity of the products formed in these NMR tube reactions was confirmed by comparison of the $^{31}P\{^1H\}$ NMR data with those of pure samples of **4a-f,h** synthesized by the conventional route, *i.e.* through the reaction of dimer [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] (**1**) with 2.2 equivalents of the corresponding secondary phosphine oxide $R_2P(=O)H$ (Scheme 5). We must note in this point that formation of [$RuCl_2(\eta^6$-*p*-cymene)(PPh_2OH)] (**4a**) by hydrolysis of **2a**,[18b] as well as by direct reaction of **1** with $Ph_2P(=O)H$,[11b] was previously described in the literature. In the case of complexes [$RuCl_2(\eta^6$-*p*-cymene)(PCy_2Cl)] (**2g**) and [$RuCl_2(\eta^6$-*p*-cymene)($PPhCl_2$)] (**3**), hydrolysis of the chlorodicyclohexylphosphine and dichlorophenylphosphine ligands also takes place in the presence of water, but the process is accompanied by an extensive decoordination of the ligand, as assessed by the appearance of additional signals in the $^{31}P\{^1H\}$ NMR spectra at δ_P 50 and 20 ppm corresponding to $Cy_2P(=O)H$[14e] and PhP(=O)H(OH),[21] respectively. Although we have no definitive explanation for these results, we assume that the partial decoordination of the *in-situ* generated ligands Cy_2POH and $PhP(OH)_2$ may be associated with the higher thermodynamic stability of their pentavalent tautomers $Cy_2P(=O)H$ and PhP(=O)H(OH).



Scheme 5 Synthesis of the arene-ruthenium(II) complexes **4a-f,h**.

The novel phosphinous acid complexes [$RuCl_2(\eta^6$-*p*-cymene)(PR_2OH)] (R = 4-C_6H_4F (**4b**), 4-$C_6H_4CF_3$ (**4c**), 4-C_6H_4Me (**4d**), 4-C_6H_4OMe (**4e**), 2-furyl (**4f**), Et (**4h**)) were characterized by elemental analyses, IR and multinuclear NMR spectroscopy, the data obtained being in fully accord with the proposed formulations (details are given in the Experimental Section). In addition, the molecular structure of **4c** could be confirmed through a single-crystal X-ray diffraction study (see Fig. 4). An interesting aspect of the structure is that, unlike what happened with complex [$RuCl_2(\eta^6$-*p*-cymene)(PCy_2Cl)] (**2g**) (Fig. 3), the bulkier substituents of the phosphorus atom are now oriented on the same side of the *p*-cymene ligand (torsion C*-Ru-P1-C11 and C*-Ru-P1-C18 angles of 45.45° and 79.43°, respectively), while the OH group points in the opposite direction (C*-Ru-P1-O1 = 162.80°). This conformation, unexpected on the basis of steric grounds, may be imposed by the intramolecular H-bond that the OH group establishes with one of the chloride ligands, albeit this interaction is relatively weak (O1-H1o = 0.82 Å, H1o-Cl2 = 2.327 Å, O1-Cl2 = 2.99 Å and O1-H1o-Cl2 = 138.34°).[22]

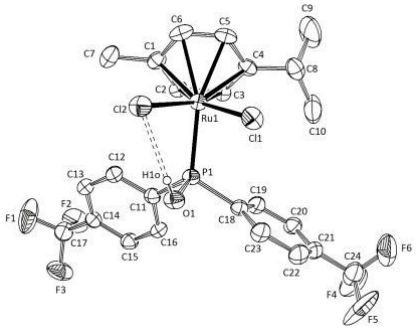
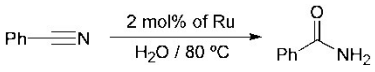


Fig 4 ORTEP-type view of the structure of complex **4c** showing the crystallographic labelling scheme. Hydrogen atoms, except that on O1, have been omitted for clarity. Thermal ellipsoids are drawn at 30% probability level. Selected bond distances (Å): Ru-P1 2.316(2), Ru-Cl1 2.388(2), Ru-Cl2 2.424(2), Ru-C* 1.7112(5), P(1)-O1 1.604(4), P1-C11 1.829(6), P1-C18 1.814(6). Selected bond angles (°): Cl1-Ru-Cl2 87.66(6), Cl1-Ru-P1 83.14(6), Cl1-Ru-C* 126.59(5), Cl2-Ru-P1 84.29(6), Cl2-Ru-C* 125.52(5), P1-Ru-C* 134.09(5), Ru-P1-O1 112.9(2), Ru-P1-C11 116.0(2), Ru-P1-C18 117.5(2), C11-P1-O1 102.1(3), C11-P1-C18 104.8(3), C18-P1-O1 101.5(3). C* denotes the centroid of the *p*-cymene ring (C1, C2, C3, C4, C5 and C6).

The ability of complexes [$RuCl_2(\eta^6$-*p*-cymene)(PR_2Cl)] (**2a-h**) and [$RuCl_2(\eta^6$-*p*-cymene)($PPhCl_2$)] (**3**) to promote the catalytic hydration of nitriles was subsequently explored employing benzonitrile as model substrate. In a typical experiment, the corresponding complex (2 mol% of Ru) was added under argon atmosphere to a 0.33 M aqueous solution of benzonitrile, and the mixture heated in an oil bath at 80 °C for 2 h. The course of the reactions was monitored by GC, analyzing aliquots every 30 min. Selected results are collected in Table 1.

Table 1 Catalytic hydration of benzonitrile using the ruthenium(II) complexes [$RuCl_2(\eta^6$-*p*-cymene)(PR_2Cl)] (**2a-h**) and [$RuCl_2(\eta^6$-*p*-cymene)($PPhCl_2$)] (**3**)[a]

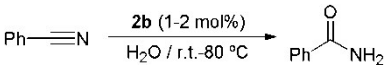


Entry	Catalyst	t (h)	Yield (%)[b]	t (h)	Yield (%)[b]
1	**2a**	0.5	90	2	> 99
2	**2b**	0.5	98	2	> 99
3	**2c**	0.5	30	2	93
4	**2d**	0.5	84	2	> 99
5	**2e**	0.5	59	2	86
6	**2f**	0.5	5	2	7
7	**2g**	0.5	14	2	40
8	**2h**	0.5	89	2	> 99
9	**3**	0.5	1	2	3

[a] Reactions were performed under Ar atmosphere starting from 1 mmol of benzonitrile (0.33 M in water). [b] Determined by GC (uncorrected GC areas).

With the exception of [$RuCl_2(\eta^6$-*p*-cymene){$P(2\text{-furyl})_2Cl$}] (**2f**), [$RuCl_2(\eta^6$-*p*-cymene)(PCy_2Cl)] (**2g**) and [$RuCl_2(\eta^6$-*p*-cymene)($PPhCl_2$)] (**3**) which showed only a residual or mederate activity (entries 6, 7 and 9), the rest of complexes were able to generate the desired benzamide as the unique reaction product in ≥ 86% GC-yield after 2 h (in no case benzoic acid was detected by GC). The low reactivity of **2g** and **3** is consistent with the NMR tube experiments discussed above, showing the extensive decoordination of the *in situ* formed phosphinous acid ligands. Regarding **2f**, its unexpected low activity does not seem to be associated with the decoordination of $P(2\text{-furyl})_2OH$ since complex [$RuCl_2(\eta^6$-*p*-cymene){$P(2\text{-furyl})_2OH$}] (**4f**) was found to be perfectly stable in solution. The presence of the potentially coordinating 2-furyl units in the ligand, which could compete with the nitrile for binding the metal, may be behind the negative result observed in this case.[23a] For the rest of complexes, a direct relationship between their catalytic activities and the electronic nature of the substituents of the *P*-donor ligands could not be drawn (entries 1-5 and 8). Taking into account that compounds [$RuCl_2(\eta^6$-*p*-cymene)(PR_2OH)] are the active species in the hydration process, two antagonistic effects come into play: (*i*) the formation of [$RuCl_2(\eta^6$-*p*-cymene)(PR_2OH)] by hydrolysis of [$RuCl_2(\eta^6$-*p*-cymene)(PR_2Cl)], that occurs faster when electron-withdrawing substituents are present in the chlorophosphine (see above), and (*ii*) the nucleophilic addition of the P-OH unit to the coordinated benzonitrile molecule, to generate the five-membered metallacyclic intermediate depicted in Scheme 1, that would be favoured when electron-donating substituents are present in the phosphinous acid ligand. Apparently, the catalytic activity observed seems to be governed by a subtle balance between these two factors. From this initial screening, complex [$RuCl_2(\eta^6$-*p*-cymene){$P(4\text{-}C_6H_4F)_2Cl$}] (**2b**) emerged as the most active, being able to generate benzamide in 98% GC-yield after only 30 min (entry 2; > 99% after 1 h).[23b] Remarkably, the *in-situ*-generated precatalyst, obtained by mixing the dimeric precursor [{$RuCl(\mu\text{-}Cl)(\eta^6$-*p*-cymene)}$_2$] (**1**) (1 mol%) with $P(4\text{-}C_6H_4F)_2Cl$ (2 mol%), presents the same catalytic performance than that of the isolated complex [$RuCl_2(\eta^6$-*p*-cymene){$P(4\text{-}C_6H_4F)_2Cl$}] (**2b**) (99% GC-yield of benzamide after 1 h). This convenient one-pot procedure, based on the use of two commercial reagents, without the need of any purification, may be particularly attractive for application by non-expert organometallic chemists.

Table 2 Catalytic hydration of benzonitrile using the ruthenium(II) complex [$RuCl_2(\eta^6$-*p*-cymene){$P(4\text{-}C_6H_4F)_2Cl$}] (**2b**): Effect of the metal loading and temperature[a]



Entry	% of Ru	T (°C)	t (h)	Yield (%)[b]
1	2 mol%	80	1	> 99
2	1 mol%	80	8	95
3	2 mol%	70	1	> 99
4	2 mol%	60	1.5	> 99
5	2 mol%	50	3	> 99
6	2 mol%	40	4	> 99
7	2 mol%	r.t.	10	> 99

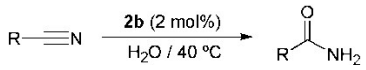
[a] Reactions were performed under Ar atmosphere starting from 1 mmol of benzonitrile (0.33 M in water). [b] Determined by GC (uncorrected GC areas).

With the isolated complex **2b** we conducted additional studies at lower metal loadings and temperatures (Table 2). Thus, while the reduction of the catalyst loading from 2 to 1 mol% resulted in a significant drop in activity (entry 2 *vs* 1), a decrease in temperature had not a dramatic effect on the

effectiveness of the process (entries 3-6). For example, performing the reaction at 40 °C, quantitative conversion was reached in 4 h (entry 6). To our delight the reaction could also be completed at r.t. in a reasonable time (10 h; entry 7). We would like to point here that such a remarkable reactivity at low temperatures is unprecedented for ruthenium catalysts.[24,25,26]

To define the scope of this catalytic transformation, other aromatic and heteroaromatic nitriles were subjected to the action of complex [$RuCl_2(\eta^6$-*p*-cymene){P(4-$C_6H_4F)_2Cl$}] (**2b**) (entries 2-16 in Table 3). Thus, we were pleased to find that all the substrates tested could be selectively converted into the corresponding primary amides in high yield (≥ 89% by GC; ≥ 75% isolated) and, in general, short times at 40 °C. Several electron-withdrawing and electron-donating functional groups in the *ortho*, *meta* and *para* positions of the aromatic rings were tolerated, and no over-hydrolysis to carboxylic acids was observed. As shown in entries 17-21, complex **2b** was also effective in the hydration of vinylic and non-conjugated nitriles, thus confirming its general applicability and the synthetic potential of this reaction. However, we must note that, due probably to its low solubility in water, with the purely aliphatic heptanenitrile an increase in temperature (100 °C) was needed to obtain the desired hexanamide in high yield (entry 20).

Table 3 Catalytic hydration of nitriles using the ruthenium(II) complex [$RuCl_2(\eta^6$-*p*-cymene){P(4-$C_6H_4F)_2Cl$}] (**2b**)[a]

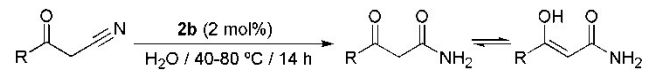


Entry	Nitrile	t (h)	Yield (%)[b]
1	R = Ph	4	> 99 (93)
2	R = 2-C_6H_4F	5	> 99 (93)
3	R = 4-C_6H_4F	2	> 99 (79)
4	R = C_6F_5	10	92 (85)
5	R = 3-C_6H_4Cl	1.5	> 99 (89)
6	R = 4-C_6H_4Cl	9.5	98 (83)
7	R = 2-C_6H_4Br	8	97 (78)
8	R = 4-C_6H_4Br	5.5	98 (91)
9	R = 4-$C_6H_4C(=O)Me$	3.5	96 (80)
10	R = 4-$C_6H_4C(=O)H$	3.5	99 (77)
11	R = 4-$C_6H_4C(=O)OEt$	8	89 (75)
12	R = 4-C_6H_4OMe	6	98 (90)
13	R = 4-C_6H_4SMe	6.5	98 (91)
14	R = 1,3-benzodioxole-5-yl	24	96 (85)
15	R = 5-Me-2-furyl	0.5	> 99 (92)
16	R = 3-thienyl	2	99 (89)
17	R = CH_2Cl	1	99 (93)
18	R = CH_2OPh	2	> 99 (96)
10	R = CH_2-2-thienyl	2	> 99 (92)
20[c]	R = *n*-C_6H_{13}	6	99 (83)
21	R = (*E*)-CH=CHPh	8	99 (95)

[a] Reactions were performed under Ar atmosphere starting from 1 mmol of the corresponding nitrile (0.33 M in water). [b] Determined by GC (uncorrected GC areas); Isolated yields after work-up are given in brackets. [c] Reaction performed at 100 °C.

The outstanding performance of complex [$RuCl_2(\eta^6$-*p*-cymene){P(4-$C_6H_4F)_2Cl$}] (**2b**) was further exploited in the catalytic synthesis of β-ketoamides by hydration of β-ketonitriles (Table 4). At this point, we would like to stress that β-ketoamides are versatile intermediates in the preparation of a large variety of heterocycles, such as lactams,[27] pyrans,[28] oxocyclohexenes,[29] isoquinolines,[30] pyrroloquinolines,[31] naphthyridines,[32] nicotinamides,[33] or 3-acyltetramic acids,[34] to name a few. In addition, they can also be easily converted, *via* a zinc-carbenoid mediated chain-extension, into their γ-keto homologues, which are compounds related with a number of biologically relevant systems.[35] Another interesting aspect in the chemistry of β-ketoamides is their use as precursors of chiral β-hydroxyamides, which are useful building blocks for the synthesis of pharmacological molecules, through the asymmetric hydrogenation of the C=O unit.[36] As a result of all this, considerable efforts have been directed towards the development of synthetic methodologies giving access to this class of compounds. In this regard, the aminolysis of β-ketoesters,[37] the addition of amines to α-acylketenes[38] and diketenes,[39] the α-acylation of amides,[40] the addition of enolates to isocyanates,[41] and the catalytic oxidation of *N*-hydroxy-propargylamines,[42] are among the most popular methods currently employed for the preparation β-ketoamides.[43] However, in most cases, these methods are only appropriate for secondary and tertiary β-ketoamides, the *N*-unsubstituted ones being hardly obtainable or non-accessible. The hydration of β-ketonitriles enables, in principle, a simple entry to primary β-ketoamides. However, the only catalytic systems described so far in the literature for this transformation are enzymatic.[44] Chemocatalytic reactions are unknown.[45]

Table 4 Catalytic hydration of β-ketonitriles using the ruthenium(II) complex [$RuCl_2(\eta^6$-*p*-cymene){P(4-$C_6H_4F)_2Cl$}] (**2b**)[a]



Entry	β-Ketonitrile	Temp. (°C)	Yield (%)[b]	K/E ratio[c]
1	R = Ph	40	77	1.6:1
2	R = 4-C_6H_4F	40	88	2.2:1
3	R = 2-C_6H_4Cl	40	75	1:1.8
4	R = 3-C_6H_4Cl	40	80	1.1:1
5	R = 4-C_6H_4Cl	40	89	1.3:1
6	R = 3,4-$C_6H_3Cl_2$	60	83	1:1
7	R = 3-$C_6H_4CF_3$	40	79	1.1:1
8	R = 3-C_6H_4Me	40	84	1.6:1
9	R = 4-C_6H_4Me	60	80	2.2:1
10	R = 4-C_6H_4OMe	60	79	4:1
11	R = 2-Br-5-C_6H_3OMe	60	90	1:1.9
12	R = 2-Furyl	40	81	4.9:1
13	R = 3-Thienyl	60	73	9.9:1
14	R = ^{t}Bu	80	71	2.2:1

[a] Reactions were performed under Ar atmosphere starting from 1 mmol of the corresponding nitrile (0.33 M in water). [b] Isolated yield. [c] Keto/enol ratio determined by ^{1}H NMR spectroscopy in DMSO-d_6.

As shown in Table 4, employing 2 mol% of complex **2b** and performing the catalytic reactions in a temperature range of 40-80 °C for 14 h,[46] a diverse family of β-ketonitriles could be converted into the corresponding β-ketoamides, in high isolated yields (71-90%), regardless of the nature of the substituent present in the keto group. As expected, the NMR spectra obtained for these amide products showed in all cases the presence of a tautomeric mixture of their keto and enol forms (see ESI).[47]

Finally we must note that inspection by $^{31}P\{^1H\}$ NMR spectroscopy of the crude reaction mixtures (after solvent removal) of some of the catalytic reactions included in Tables 3 and 4 confirms that, during the catalytic events, complex [$RuCl_2(\eta^6$-*p*-cymene){P(4-$C_6H_4F)_2Cl$}] (**2b**) is completely converted into the active compound [$RuCl_2(\eta^6$-*p*-cymene){P(4-$C_6H_4F)_2OH$}] (**4b**), the spectra showing a major resonance at δ_P = 106 ppm. A minor singlet signal at δ_P = 18 ppm, corresponding to (4-$C_6H_4F)_2P(=O)H$,[15e] is additionally observed in the spectra indicating that partial dissociation of the *P*-donor ligand is also taking place.

Conclusions

In summary, we have demonstrated that simple, commercially available, and inexpensive chlorophosphines can be used as effective auxiliary ligands in metal-catalyzed nitrile hydration reactions. In aqueous medium, the coordinated chlorophosphines readily undergo hydrolysis to generate the corresponding phosphinous acids PR_2OH, which are well-known "cooperative" ligands for this catalytic transformation. In particular, using the arene-ruthenium(II) complex [$RuCl_2(\eta^6$-*p*-cymene){P(4-$C_6H_4F)_2Cl$}] (**2b**) we could develop a new protocol for the high-yield and selective conversion of nitriles into primary amides, in pure water as a solvent, and at unusually low temperatures. The synthetic utility of the methodology reported herein was fully validated with the preparation of a diverse family of β-ketoamides, representing the first chemocatalytic route reported in the literature to access to this relevant class of compounds from β-ketonitriles.

Experimental

General methods

The manipulations were performed under argon atmosphere using vacuum-line and standard Schlenk or sealed-tube techniques. All reagents were obtained from commercial suppliers and used as received, with the exception of compounds [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] (**1**)[48] and [$RuCl_2(\eta^6$-*p*-cymene)(PPh_2OH)] (**4a**)[11b] which were prepared following the method reported in the literature. GC measurements were performed with a Hewlett-Packard HP6890 equipment using a Supelco Beta-Dex™ 120 column (30 m length; 250 µm diameter). Elemental analyses were provided by the Analytical Service of the Instituto de Investigaciones Químicas (IIQ-CSIC) of Seville. Infrared spectra were recorded on a Perkin-Elmer 1720-XFT spectrometer. NMR spectra were recorded on Bruker DPX-300 or AV400 instruments. The chemical shift values (δ) are given in parts per million and are referred to the residual peak of the deuterated solvent employed (^1H and ^{13}C), to an external 85% aqueous H_3PO_4 solution (^{31}P), or to the $CFCl_3$ standard (^{19}F). DEPT experiments have been carried out for all the compounds reported.

Synthesis of [$RuCl_2(\eta^6$-*p*-cymene)(PR_2Cl)] (R = Ph (2a), 4-C_6H_4F (2b), 4-$C_6H_4CF_3$ (2c), 4-C_6H_4Me (2d), 4-C_6H_4OMe (2e), 2-furyl (2f), Cy (2g), Et (2h))

A suspension of the dimeric precursor [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] (**1**) (0.165 g, 0.27 mmol) in tetrahydrofuran (15 mL) was treated, at room temperature, with the appropriate chlorophosphine (0.57 mmol) for 1 h. The solvent was then removed under reduced pressure, and the resulting orange-red solid residue washed with hexanes (3 x 20 mL), and dried in vacuo. **(2a):**[18] Yield: 0.230 g (81%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 96.6 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 7.97-7.44 (m, 10H, Ph), 5.41 and 5.36 (d, 2H each, $^3J_{HH}$ = 6.0 Hz, CH of cym), 2.84 (sept, 1H, $^3J_{HH}$ = 6.0 Hz, C*H*Me_2), 2.02 (s, 3H, Me), 1.21 (d, 6H, $^3J_{HH}$ = 6.0 Hz, CH*Me*$_2$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 135.9 (d, $^1J_{PC}$ = 36.2 Hz, C_{ipso} of Ph), 132.9 (d, J_{PC} = 12.1 Hz, CH_{ortho} or CH_{meta} of Ph), 131.4 (s, CH_{para} of Ph), 127.9 (d, J_{PC} = 10.1 Hz, CH_{ortho} or CH_{meta} of Ph), 110.8 and 98.4 (s, C of cym), 91.6 (d, $^2J_{PC}$ = 5.0 Hz, CH of cym), 88.3 (d, $^2J_{PC}$ = 6.0 Hz, CH of cym), 30.5 (s, *C*HMe_2), 21.7 (s, CH*Me*$_2$), 17.6 (s, Me) ppm. Elemental analysis calcd. (%) for $C_{22}H_{24}Cl_3PRu$: C 50.16, H 4.59; found: C 50.27, H 4.69. **(2b):** Yield: 0.264 g (87%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 94.4 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 7.93 and 7.19 (m, 4H each, C_6H_4F), 5.43 and 5.36 (d, 2H each, $^3J_{HH}$ = 6.0 Hz, CH of cym), 2.86 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, C*H*Me_2), 2.03 (s, 3H, Me), 1.22 (d, 6H, $^3J_{HH}$ = 6.9 Hz, CH*Me*$_2$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 164.0 (dd, $^1J_{FC}$ = 253.4 Hz, $^4J_{PC}$ = 2.5 Hz, C of C_6H_4F), 135.5 (dd, $^2J_{PC}$ = 13.4 Hz, $^3J_{FC}$ = 8.8 Hz, CH of C_6H_4F), 131.2 (dd, $^1J_{PC}$ = 39.3 Hz, $^4J_{FC}$ = 3.4 Hz, C of C_6H_4F), 115.8 (dd, $^2J_{FC}$ = 21.6 Hz, $^3J_{PC}$ = 12.1 Hz, CH of C_6H_4F), 111.2 and 98.8 (s, C of cym), 91.4 (d, $^2J_{PC}$ = 4.6 Hz, CH of cym), 88.4 (d, $^2J_{PC}$ = 6.4 Hz, CH of cym), 30.6 (s, *C*HMe_2), 21.6 (s, CH*Me*$_2$), 17.6 (s, Me) ppm. $^{19}F\{^1H\}$ NMR (CD_2Cl_2): δ = -108.2 (d, $^4J_{PF}$ = 2.3 Hz) ppm. Elemental analysis calcd. (%) for $C_{22}H_{22}Cl_3F_2PRu$: C 46.95, H 3.94; found: C 46.82, H 4.02. **(2c):** Yield: 0.207 g (58%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 93.5 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 8.09 (dd, 4H, $^3J_{PH}$ = 10.5 Hz, $^3J_{HH}$ = 8.6 Hz, $C_6H_4CF_3$), 7.70 (dd, 4H, $^3J_{HH}$ = 8.6 Hz, $^4J_{PH}$ = 1.8 Hz, $C_6H_4CF_3$), 5.50 and 5.42 (d, 2H each, $^3J_{HH}$ = 6.1 Hz, CH of cym), 2.87 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, C*H*Me_2), 2.06 (s, 3H, Me), 1.23 (d, 6H, $^3J_{HH}$ = 6.9 Hz, CH*Me*$_2$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 139.1 (d, $^1J_{PC}$ = 34.9 Hz, C of $C_6H_4CF_3$), 133.5 (d, $^2J_{PC}$ = 12.0 Hz, CH of $C_6H_4CF_3$), 132.8 (q, $^2J_{FC}$ = 32.7 Hz, C of $C_6H_4CF_3$), 124.8 (dq, $^3J_{PC}$ = 10.8 Hz, $^3J_{FC}$ = 3.7 Hz, CH of $C_6H_4CF_3$), 123.5 (q, $^1J_{FC}$ = 272.5 Hz, CF_3), 111.6 and 99.5 (s, C of cym), 91.3 (d, $^2J_{PC}$ = 4.4 Hz, CH of cym), 88.7 (d, $^2J_{PC}$ = 6.0 Hz, CH of cym), 30.6 (s, *C*HMe_2), 21.6 (s, CH*Me*$_2$), 17.7 (s, Me) ppm. $^{19}F\{^1H\}$ NMR (CD_2Cl_2): δ = -63.5 (s) ppm. Elemental analysis calcd. (%) for $C_{24}H_{22}F_6Cl_3PRu$: C 43.49, H 3.35; found: C 43.60, H 3.42. **(2d):** Yield: 0.228 g (76%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 97.3 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 7.78 (dd, 4H, $^3J_{PH}$ = 11.4 Hz, $^3J_{HH}$ = 8.3 Hz, C_6H_4Me), 7.25 (dd, 4H, $^3J_{HH}$ = 8.3 Hz, $^4J_{PH}$ = 2.4 Hz, C_6H_4Me), 5.39 and 5.34 (d, 2H each, $^3J_{HH}$ = 6.3 Hz, CH of cym), 2.84 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, C*H*Me_2), 2.41 (s, 6H, C_6H_4Me), 2.02 (s, 3H, Me), 1.21 (d, 6H, $^3J_{HH}$ = 6.9 Hz, CH*Me*$_2$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 142.1 (s, C of C_6H_4Me), 132.9 (d, J_{PC} = 12.0 Hz, CH of C_6H_4Me), 132.5 (d, $^1J_{PC}$ = 38.2 Hz, C of C_6H_4Me), 128.5 (d, J_{PC} = 11.0 Hz, CH of C_6H_4Me), 110.6 and 98.2 (s, C of cym), 91.5 (d, $^2J_{PC}$ = 4.4 Hz, CH of cym), 88.2 (d, $^2J_{PC}$ = 6.2 Hz, CH of cym), 30.5 (s,

*C*HMe$_2$), 21.7 (s, CH*Me*$_2$), 21.2 (s, C$_6$H$_4$*Me*), 17.6 (s, Me) ppm. Elemental analysis calcd. (%) for $C_{24}H_{28}Cl_3PRu$: C 51.95, H 5.09; found: C 51.80, H 5.22. **(2e):** Yield: 0.310 g (98%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 96.6 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 7.86-7.79 (m, 4H, C$_6$*H*$_4$OMe), 6.94 (dd, 4H, $^3J_{HH}$ = 9.0 Hz, $^4J_{PH}$ = 1.4 Hz, C$_6$*H*$_4$OMe), 5.39 and 5.33 (d, 2H each, $^3J_{HH}$ = 6.3 Hz, CH of cym), 3.87 (s, 6H, OMe), 2.85 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, C*H*Me$_2$), 2.02 (s, 3H, Me), 1.22 (d, 6H, $^3J_{HH}$ = 6.9 Hz, CH*Me*$_2$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 162.0 (s, C of C$_6$H$_4$OMe), 134.8 (d, J_{PC} = 13.3 Hz, CH of C$_6$H$_4$OMe), 126.9 (d, $^1J_{PC}$ = 41.9 Hz, C of C$_6$H$_4$OMe), 113.2 (d, J_{PC} = 11.9 Hz, CH of C$_6$H$_4$OMe), 110.6 and 98.0 (s, C of cym), 91.4 (d, $^2J_{PC}$ = 4.4 Hz, CH of cym), 88.1 (d, $^2J_{PC}$ = 6.2 Hz, CH of cym), 55.4 (s, OMe), 30.5 (s, *C*HMe$_2$), 21.6 (s, CH*Me*$_2$), 17.6 (s, Me) ppm. Elemental analysis calcd. (%) for $C_{24}H_{28}Cl_3O_2PRu$: C 49.12, H 4.81; found: C 49.27, H 4.82. **(2f):** Yield: 0.235 g (86%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 55.6 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 7.79 (br, 2H, CH of furyl), 7.25 (d, 2H, $^3J_{HH}$ = 3.6 Hz, CH of furyl), 6.58 (m, 2H, CH of furyl), 5.70 and 5.64 (d, 2H each, $^3J_{HH}$ = 6.0 Hz, CH of cym), 2.84 (sept, 1H, $^3J_{HH}$ = 7.1 Hz, C*H*Me$_2$), 2.08 (s, 3H, Me), 1.18 (d, 6H, $^3J_{HH}$ = 7.1 Hz, CH*Me*$_2$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 148.3 (d, $^3J_{PC}$ = 6.3 Hz, CH of furyl), 145.9 (d, $^1J_{PC}$ = 65.6 Hz, C of furyl), 125.1 (d, $^2J_{PC}$ = 19.1 Hz, CH of furyl), 111.5 (d, $^3J_{PC}$ = 7.3 Hz, CH of furyl), 111.0 and 99.1 (s, C of cym), 91.8 (d, $^2J_{PC}$ = 5.8 Hz, CH of cym), 88.2 (d, $^2J_{PC}$ = 7.0 Hz, CH of cym), 30.5 (s, *C*HMe$_2$), 21.4 (s, CH*Me*$_2$), 17.6 (s, Me) ppm. Elemental analysis calcd. (%) for $C_{18}H_{20}Cl_3O_2PRu$: C 42.66, H 3.98; found: C 42.80, H 4.16. **(2g):** Yield: 0.227 g (78%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 155.7 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 5.47 (br, 4H, CH of cym), 2.97 (sept, 1H, $^3J_{HH}$ = 7.5 Hz, C*H*Me$_2$), 2.80-2.60 (m, 2H, CH of Cy), 2.14 (s, 3H, Me), 1.90-1.60 (m, 14H, CH$_2$), 1.30-1.26 (m, 6H, CH$_2$), 1.26 (d, 6H, $^3J_{HH}$ = 7.5 Hz, CH*Me*$_2$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 106.6 and 98.5 (s, C of cym), 90.6 (d, $^2J_{PC}$ = 5.0 Hz, CH of cym), 89.5 (d, $^2J_{PC}$ = 4.0 Hz, CH of cym), 40.7 (d, $^2J_{PC}$ = 9.0 Hz, CH of Cy), 29.9 (s, *C*HMe$_2$), 27.1 and 25.8 (s, CH$_2$), 26.6 (d, J_{PC} = 13.0 Hz, CH$_2$), 26.5 (d, J_{PC} = 11.0 Hz, CH$_2$), 25.9 (d, J_{PC} = 3.0 Hz, CH$_2$), 21.7 (s, CH*Me*$_2$), 17.5 (s, Me) ppm. Elemental analysis calcd. (%) for $C_{22}H_{36}Cl_3PRu$: C 49.03, H 6.73; found: C 48.93, H 6.90. **(2h):** Yield: 0.188 g (81%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 135.7 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 5.56 and 5.54 (d, 2H each, $^3J_{HH}$ = 6.9 Hz, CH of cym), 2.88 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, C*H*Me$_2$), 2.62-2.32 (m, 4H, CH$_2$), 2.14 (s, 3H, Me), 1.25 (d, 6H, $^3J_{HH}$ = 6.9 Hz, CH*Me*$_2$), 1.23 (dt, $^3J_{PH}$ = 18.0 Hz, $^3J_{HH}$ = 7.5 Hz, CH$_2$C*H*$_3$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 108.1 and 97.6 (s, C of cym), 90.1 (d, $^2J_{PC}$ = 5.1 Hz, CH of cym), 87.8 (d, $^2J_{PC}$ = 5.7 Hz, CH of cym), 30.4 (s, *C*HMe$_2$), 25.5 (d, $^1J_{PC}$ = 18.2 Hz, CH$_2$), 21.7 (s, CH*Me*$_2$), 17.8 (s, Me), 7.8 (d, $^2J_{PC}$ = 5.0 Hz, CH$_2$*C*H$_3$) ppm. Elemental analysis calcd. (%) for $C_{14}H_{24}Cl_3PRu$: C 39.04, H 5.62; found: C 39.15, H 5.74.

Synthesis of [RuCl$_2$(η^6-*p*-cymene)(PPhCl$_2$)] (3)

A suspension of the dimeric precursor [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] (**1**) (0.165 g, 0.27 mmol) in tetrahydrofuran (15 mL) was treated, at room temperature, with dichlorophenylphosphine (0.077 mL, 0.57 mmol) for 15 min. The orange solid precipitated formed was filtered, washed with diethyl ether (3 x 20 mL), and dried in vacuo. Yield: 0.196 g (75%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 145.6 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 8.13-7.51 (m, 5H, Ph), 5.36 (br, 4H, CH of cym), 2.89 (sept, 1H, $^3J_{HH}$ = 6.0 Hz, C*H*Me$_2$), 2.13 (s, 3H, Me), 1.25 (d, 6H, $^3J_{HH}$ = 6.0 Hz, CH*Me*$_2$) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 138.1 (d, $^1J_{PC}$ = 20.1 Hz, C$_{ipso}$ of Ph), 132.6 (s, CH$_{para}$ of Ph), 131.4 (d, J_{PC} = 13.1 Hz, CH$_{ortho}$ or CH$_{meta}$ of Ph), 127.9 (d, J_{PC} = 12.1 Hz, CH$_{ortho}$ or CH$_{meta}$ of Ph), 112.2 and 100.3 (s, C of cym), 92.7 (d, $^2J_{PC}$ = 6.0 Hz, CH of cym), 89.2 (d, $^2J_{PC}$ = 7.0 Hz, CH of cym), 30.7 (s, *C*HMe$_2$), 21.5 (s, CH*Me*$_2$), 17.8 (s, Me) ppm. Elemental analysis calcd. (%) for $C_{16}H_{19}Cl_4PRu$: C 39.61, H 3.95; found: C 39.51, H 4.08.

Synthesis of [RuCl$_2$(η^6-*p*-cymene)(PR$_2$OH)] (R = 4-C$_6$H$_4$F (4b), 4-C$_6$H$_4$CF$_3$ (4c), 4-C$_6$H$_4$Me (4d), 4-C$_6$H$_4$OMe (4e), 2-furyl (4f), Et (4h))

The dimeric precursor [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] (**1**) (0.165 g, 0.27 mmol) was added, at room temperature, to a tetrahydrofuran solution (15 mL) containing the appropriate secondary phosphine oxide R$_2$P(=O)H, generated *in situ* by reacting the corresponding chlorophosphine PR$_2$Cl (0.59 mmol) with H$_2$O (17 μL, 0.092 mmol) for 1 h.[17] The resulting mixture was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure, and the resulting orange-red solid residue washed with hexane (3 x 20 mL; complexes **4c-e,h**) or a mixture diethyl ether/hexane (1:1 v/v; 3 x 20 mL; complexes **4b,f**), and dried in vacuo. Complexes **4d** and **4h** required further purification by column chromatography over SiO$_2$, employing CH$_2$Cl$_2$ as the eluent. **(4b):** Yield: 0.250 g (85%). IR (KBr): ν = 3145 (w, O-H) cm^{-1}. $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 106.1 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 7.70 and 7.23 (m, 4H each, C$_6$H$_4$F), 5.40 and 5.30 (d, 2H each, $^3J_{HH}$ = 5.7 Hz, CH of cym), 2.53 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, C*H*Me$_2$), 2.01 (s, 3H, Me), 1.03 (d, 6H, $^3J_{HH}$ = 6.9 Hz, CH*Me*$_2$) ppm; OH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 164.5 (d, $^1J_{FC}$ = 250.3 Hz, C of C$_6$H$_4$F), 133.9 (dd, $^2J_{PC}$ = 13.1 Hz, $^3J_{FC}$ = 8.6 Hz, CH of C$_6$H$_4$F), 133.2 (d, $^1J_{PC}$ = 62.6 Hz, C of C$_6$H$_4$F), 115.6 (dd, $^2J_{FC}$ = 21.4 Hz, $^3J_{PC}$ = 11.8 Hz, CH of C$_6$H$_4$F), 109.0 and 97.3 (s, C of cym), 89.3 (d, $^2J_{PC}$ = 4.5 Hz, CH of cym), 87.1 (d, $^2J_{PC}$ = 5.4 Hz, CH of cym), 30.4 (s, *C*HMe$_2$), 21.5 (s, CH*Me*$_2$), 17.6 (s, Me) ppm. $^{19}F\{^1H\}$ NMR (CD_2Cl_2): δ = -108.6 (d, $^4J_{PF}$ = 2.0 Hz) ppm. Elemental analysis calcd. (%) for $C_{22}H_{23}Cl_2F_2OPRu$: C 48.54, H 4.26; found: C 48.40, H 4.11. **(4c):** Yield: 0.181 g (52%). IR (KBr): ν = 3185 (w, O-H) cm^{-1}. $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 105.9 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 7.88-7.79 (m, 8H, C$_6$H$_4$CF$_3$), 5.46 and 5.32 (d, 2H each, $^3J_{HH}$ = 5.8 Hz, CH of cym), 2.50 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, C*H*Me$_2$), 2.05 (s, 3H, Me), 1.02 (d, 6H, $^3J_{HH}$ = 6.9 Hz, CH*Me*$_2$) ppm; OH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 141.2 (d, $^1J_{PC}$ = 54.6 Hz, C of C$_6$H$_4$CF$_3$), 132.8 (q, $^2J_{FC}$ = 31.6 Hz, C of C$_6$H$_4$CF$_3$), 131.8 (d, $^2J_{PC}$ = 12.0 Hz, CH of C$_6$H$_4$CF$_3$), 125.3 (dq, $^3J_{PC}$ = 10.8 Hz, $^3J_{FC}$ = 3.7 Hz, CH of C$_6$H$_4$CF$_3$), 123.7 (q, $^1J_{FC}$ = 272.9 Hz, CF$_3$), 109.2 and 98.0 (s, C of cym), 89.4 (d, $^2J_{PC}$ = 4.6 Hz, CH of cym), 87.5 (d, $^2J_{PC}$ = 5.3 Hz, CH of cym), 30.5 (s, *C*HMe$_2$), 21.4 (s, CH*Me*$_2$), 17.7 (s, Me) ppm. $^{19}F\{^1H\}$ NMR (CD_2Cl_2): δ = -63.4 (s) ppm. Elemental analysis calcd. (%) for $C_{24}H_{23}F_6Cl_2OPRu$: C 44.74, H 3.60; found: C 44.63, H 3.53. **(4d):** Yield: 0.165 g (57%). IR (KBr): ν =

3037 (w, O-H) cm^{-1}. $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 106.8 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 7.58 (dd, 4H, $^3J_{PH}$ = 10.8 Hz, $^3J_{HH}$ = 8.0 Hz, C_6H_4Me), 7.33 (dd, 4H, $^3J_{HH}$ = 8.0 Hz, $^4J_{PH}$ = 1.8 Hz, C_6H_4Me), 5.38 and 5.27 (d, 2H each, $^3J_{HH}$ = 5.6 Hz, CH of cym), 2.50 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, $CHMe_2$), 2.45 (s, 6H, C_6H_4Me), 1.99 (s, 3H, Me), 1.02 (d, 6H, $^3J_{HH}$ = 6.9 Hz, $CHMe_2$) ppm; OH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 141.6 (d, $^4J_{PC}$ = 2.3 Hz, C of C_6H_4Me), 134.3 (d, $^1J_{PC}$ = 59.8 Hz, C of C_6H_4Me), 131.4 (d, J_{PC} = 12.0 Hz, CH of C_6H_4Me), 128.9 (d, J_{PC} = 11.0 Hz, CH of C_6H_4Me), 108.4 and 99.6 (s, C of cym), 89.3 (d, $^2J_{PC}$ = 5.0 Hz, CH of cym), 86.8 (d, $^2J_{PC}$ = 5.8 Hz, CH of cym), 30.6 (s, $CHMe_2$), 21.5 (s, $CHMe_2$), 21.2 (s, C_6H_4Me), 17.5 (s, Me) ppm. Elemental analysis calcd. (%) for $C_{24}H_{29}Cl_2OPRu$: C 53.74, H 5.45; found: C 53.61, H 5.50. **(4e):** Yield: 0.301 g (98%). IR (KBr): ν = 3196 (w, O-H) cm^{-1}. $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 105.9 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 7.63 (dd, 4H, $^3J_{PH}$ = 10.2 Hz, $^3J_{HH}$ = 8.0 Hz, C_6H_4OMe), 7.03 (dd, 4H, $^3J_{HH}$ = 8.6 Hz, $^4J_{PH}$ = 1.5 Hz, C_6H_4OMe), 5.38 and 5.28 (d, 2H each, $^3J_{HH}$ = 5.7 Hz, CH of cym), 3.89 (s, 6H, OMe), 2.55 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, $CHMe_2$), 1.99 (s, 3H, Me), 1.03 (d, 6H, $^3J_{HH}$ = 6.9 Hz, $CHMe_2$) ppm; OH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 161.9 (s, C of C_6H_4OMe), 133.5 (d, J_{PC} = 13.0 Hz, CH of C_6H_4OMe), 128.9 (d, $^1J_{PC}$ = 62.9 Hz, C of C_6H_4OMe), 113.6 (d, J_{PC} = 11.7 Hz, CH of C_6H_4OMe), 108.4 and 96.4 (s, C of cym), 89.3 (d, $^2J_{PC}$ = 4.6 Hz, CH of cym), 86.8 (d, $^2J_{PC}$ = 5.6 Hz, CH of cym), 55.5 (s, OMe), 30.4 (s, $CHMe_2$), 21.5 (s, $CHMe_2$), 17.6 (s, Me) ppm. Elemental analysis calcd. (%) for $C_{24}H_{29}O_3Cl_2PRu$: C 50.71, H 5.14; found: C 50.56, H 5.12. **(4f):** Yield: 0.224 g (85%). IR (KBr): ν = 3125 (w, O-H) cm^{-1}. $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 78.1 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 7.70 (br, 2H, CH of furyl), 7.05 (d, 2H, $^3J_{HH}$ = 3.0 Hz, CH of furyl), 6.63 (br, 2H, CH of furyl), 5.57 (br, 4H, CH of cym), 2.65 (sept, 1H, $^3J_{HH}$ = 6.9 Hz, $CHMe_2$), 2.03 (s, 3H, Me), 1.10 (d, 6H, $^3J_{HH}$ = 7.1 Hz, $CHMe_2$) ppm; OH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 150.0 (d, $^1J_{PC}$ = 90.3 Hz, C of furyl), 147.6 (d, $^3J_{PC}$ = 6.7 Hz, CH of furyl), 121.4 (d, $^2J_{PC}$ = 15.9 Hz, CH of furyl), 111.2 (d, $^3J_{PC}$ = 6.7 Hz, CH of furyl), 108.7 and 97.3 (s, C of cym), 90.1 (d, $^2J_{PC}$ = 5.4 Hz, CH of cym), 86.9 (d, $^2J_{PC}$ = 6.3 Hz, CH of cym), 30.6 (s, $CHMe_2$), 21.4 (s, $CHMe_2$), 17.8 (s, Me) ppm. Elemental analysis calcd. (%) for $C_{18}H_{21}O_3Cl_2PRu$: C 44.28, H 4.33; found: C 44.37, H 4.45. **(4h):** Yield: 0.129 g (58%). IR (KBr): ν = 3180 (w, O-H) cm^{-1}. $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ = 126.6 (s) ppm. ^1H NMR (CD_2Cl_2): δ = 5.54 and 5.50 (d, 2H each, $^3J_{HH}$ = 5.8 Hz, CH of cym), 2.76 (sept, 1H, $^3J_{HH}$ = 7.2 Hz, $CHMe_2$), 2.28-2.21 (m, 4H, CH_2), 2.09 (s, 3H, Me), 1.26 (d, 6H, $^3J_{HH}$ = 7.2 Hz, $CHMe_2$), 1.23 (dt, $^3J_{PH}$ = 16.2 Hz, $^3J_{HH}$ = 7.6 Hz, CH_2CH_3) ppm; OH signal not observed. $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ = 106.8 and 95.0 (s, C of cym), 89.2 (d, $^2J_{PC}$ = 4.5 Hz, CH of cym), 85.6 (d, $^2J_{PC}$ = 5.4 Hz, CH of cym), 30.8 (s, $CHMe_2$), 25.2 (d, $^1J_{PC}$ = 33.9 Hz, CH_2), 21.8 (s, $CHMe_2$), 18.1 (s, Me), 6.7 (d, $^2J_{PC}$ = 3.7 Hz, CH_2CH_3) ppm. Elemental analysis calcd. (%) for $C_{14}H_{25}Cl_2OPRu$: C 40.78, H 6.11; found: C 40.61, H 6.27.

General procedure for the catalytic hydration of nitriles with [$RuCl_2(\eta^6$-*p*-cymene){P(4-$C_6H_4F)_2Cl$}] (2b)

The corresponding nitrile (1 mmol), water (3 mL), and the ruthenium(II) complex **2b** (0.011 g, 0.02 mmol; 2 mol%) were introduced into a Teflon-capped sealed tube, and the reaction mixture stirred at 40 °C for the indicated time (see Table 3). The course of the reaction was monitored regularly taking samples of *ca.* 20 μL, which, after extraction with CH_2Cl_2 (3 mL), were analyzed by GC. Once the reaction finished, the hot mixture was allowed to reach room temperature, and then kept in an ice bath for 4 h. This led to the complete crystallization of the corresponding primary amide, which was separated, recrystallized from hot water, washed with hexane (2 × 5 mL) and vacuum-dried (in some cases an additional purification by column chromatography over silica gel was needed). The identity of the isolated amides was assessed by comparison of their NMR spectroscopic data with those reported in the literature (copies of the NMR spectra obtained are giving in the ESI file).

General procedure for the catalytic hydration of β-ketonitriles with [$RuCl_2(\eta^6$-*p*-cymene){P(4-$C_6H_4F)_2Cl$}] (2b)

The corresponding β-ketonitrile (1 mmol), water (3 mL), and the ruthenium(II) complex **2b** (0.011 g, 0.02 mmol; 2 mol%) were introduced into a Teflon-capped sealed tube, and the reaction mixture stirred at 40-80 °C for 14 h (see Table 4). Precipitation of the β-ketoamide formed along the reaction was observed. After that time, the hot mixture was allowed to reach room temperature, the precipitated β-ketoamide was filtered, washed with water (3 × 5 mL) and hexane (2 × 5 mL), and vacuum-dried. The identity of the isolated amides was assessed by comparison of their NMR spectroscopic data with those reported in the literature (copies of the NMR spectra obtained are giving in the ESI file).

X-Ray crystal structure determination of complexes 2g and 4c

Crystals of **2g** and **4c** suitable for X-ray diffraction analysis were obtained by slow diffusion of diethyl ether and *n*-hexane, respectively, into saturated solutions of the complexes in dichloromethane. The most relevant crystal and refinement data are collected in Table 5. In both cases, data collection was performed with an Oxford Diffraction Xcalibur Nova single crystal diffractometer using Cu-Kα radiation (λ = 1.5418 Å). Images were collected at a fixed crystal-to-detector distance of 62 mm for complex **2g** and 63 mm for **4c**, using the oscillation method with 1° oscillation and 1.5-5.0 s variable exposure time per image for **2g**, and 3.0-20.0 s for **4c**. Data collection strategy was calculated with the program CrysAlis Pro CCD.[49] Data reduction and cell refinement was performed with the program CrysAlis Pro RED.[49] An empirical absorption correction was applied using the SCALE3 ABSPACK algorithm as implemented in the program CrysAlis Pro RED.[49]

In both cases, the software package WINGX was used for space group determination, structure solution, and refinement.[50] For **2g** the structure was solved by a charge flipping iterative algorithm using SUPERFLIP,[51] and for **4c** the structure was solved by Patterson interpretation and phase expansion using DIRDIF2008.[52] Isotropic least-squares refinement on F^2 using SHELXL97 was performed.[53] During the

final stages of the refinements, all the positional parameters and the anisotropic temperature factors of all non-H atoms were refined. Complex **4c** contains two highly disordered trifluoromethyl groups. Although SHELXL97 provides two possible sites for each of the fluorine atoms, the anisotropic motion of the atoms on a single position leads to a better description of this positional disorder. The H atoms were geometrically located and their coordinates were refined riding on their parent atoms. The final position of the hydrogen atom H1o (complex **4c**) was obtained after a rotating group refinement (the initial torsion angle is derived from a difference Fourier synthesis). The function minimized was $\{\Sigma[\omega(F_o^2 - F_c^2)^2]/\Sigma[\omega(F_o^2)^2]\}^{1/2}$ where $\omega = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ (a and b values are collected in Table 5) with $\sigma(F_o^2)$ from counting statistics and $P = [\text{Max}\ (F_o^2,0) + 2F_c^2]/3$. Atomic scattering factors were taken from International Tables for X-ray Crystallography.[54] Geometrical calculations were made with PARST.[55] The crystallographic plots were made with ORTEP3.[50]

Table 5 Crystal data and structure refinement for compounds **2g** and **4c**

	2g	**4c**
Empirical formula	$C_{22}H_{36}Cl_3PRu$	$C_{24}H_{23}F_6Cl_2OPRu$
Formula weight	538.90	644.36
Temperature/K	293(2)	293(2)
Wavelength/Å	1.54184	1.54184
Crystal system	Triclinic	Monoclinic
Space group	*P*-1	$P2_1/c$
Crystal size/mm	0.19 x 0.09 x 0.03	0.52 x 0.04 x 0.04
a/Å	7.6344(3)	6.8231(1)
b/Å	10.5128(3)	11.2772(2)
c/Å	15.3514(6)	33.5183(6)
α (°)	103.182(3)	90
β (°)	92.237(3)	91.031(1)
γ (°)	90.962(3)	90
Z	2	4
Volume/Å^3	1198.29(8)	2578.66(8)
Calculated density/g cm^{-3}	1.494	1.660
μ/mm^{-1}	9.030	7.961
F(000)	556	1288
ϑ range/°	4.32-69.68	4.14-69.49
Index ranges	$-8 \le h \le 9$	$-5 \le h \le 8$
	$-12 \le k \le 9$	$-13 \le k \le 13$
	$-17 \le l \le 18$	$-40 \le l \le 40$
Completeness to ϑ_{max}	97.5%	99.3%
No. of reflns. collected	9679	21368
No. of unique reflns.	4410 (R_{int} = 0.040)	4804 (R_{int} = 0.038)
No. of parameters/restraints	244/0	317/0
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.060	1.170
Weight function (a, b)	0.0480, 0.0973	0.0203, 12.0241
R_1 [$I > 2\sigma(I)$][a]	0.0335	0.0528
wR_2 [$I > 2\sigma(I)$][a]	0.0842	0.1227
R_1 (all data)	0.0388	0.0560
R_2 (all data)	0.0920	0.1241
Largest diff. peak and hole/e Å^{-3}	0.65, -0.77	0.78, -0.57

[a] $R_1 = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

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The utility of chlorophosphines as auxiliary ligands in metal-catalyzed nitrile hydration reactions has been demonstrated, along with their application in the preparation of *β*-ketoamides.