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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 areneruthenium(II) complexes containing commercially available chlorophosphines as auxiliary ligands, *i.e.* compounds $[RuCl_2(\eta^6-p-cymene)(PR_2Cl)]$ (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 wellknown "cooperative" ligands for this catalytic transformation. Among the complexes employed, best results were obtained with $[RuCl_2(\eta^6-p-cymene){P(4-C_6H_4F)_2Cl}]$. 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 $[RuCl_2(\eta^6-p-cymene){P(4-C_6H_4F)_2Cl}]$ in the preparation of synthetically useful β -ketoamides is also presented.

Introduction

Hydration of nitriles (RC≡N) to the corresponding primary amides (RC(=O)NH₂) 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 lubricants, pharmaceuticals, production of polymers, 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{(PMe₂O)₂H}(PMe₂OH)] (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{(PR₂O)₂H}(PR₂OH)] (R₂ = chiral binaphthyl unit) complex in the kinetic resolution of racemic nitriles.¹⁰



Fig 1 Structure of the platinum(II) complex [PtH{(PMe₂O)₂H}(PMe₂OH)] (A).

The utility of phosphinous acid PR₂OH 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

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DFT calculations performed by our group with the areneruthenium(II) complexes **B** unravelled the key role played by the PR₂OH 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 $\mathsf{PR}_2\mathsf{OH}$ 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 PR₂OH ligands involves the reaction of the corresponding metallic precursor with a secondary phosphine oxide R₂P(=O)H.^{13,14} For example, complexes **A-C** were obtained from the reactions of [Pt(PPh₃)₄], [{RuCl(μ -Cl)(η^6 arene)}₂] and [{RuCl(μ -Cl)(η^3 : η^3 -C₁₀H₁₆)}₂] (C₁₀H₁₆ = 2,7dimethylocta-2,6-diene-1,8-diyl), respectively, with R₂P(=O)H (R = Me, Ph).^{8,11a,c,d} In solution, the secondary phosphine oxides exist as a tautomeric mixture of penta-, *i.e.* R₂P(=O)H, and trivalent, *i.e.* PR₂OH, isomers, with the pentavalent one predominating under ambient conditions.¹⁵ In the presence of a metal this equilibrium is driven towards the PR₂OH tautomer via coordination (Scheme 2).¹³

Scheme 2 General procedure to obtain metal complexes with PR₂OH 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 $\mathsf{PR}_2\mathsf{OH}$ 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 PR₂OH ligands. This point would be of high practical interest because, unlike the

phosphine oxides, secondarv а large number Online chlorophosphines are currently commercially03aVaflable14at 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 [RuCl₂(η° -pcymene)(PR₂Cl)] (R = aryl, heteroaryl or alkyl group). As a result of this study, we present herein a new catalytic system, i.e. complex [RuCl₂(η^6 -*p*-cymene){P(4-C₆H₄F)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 [RuCl₂(η^6 -p-cymene)(PR₂Cl)] complexes **2a-h** through the treatment of the dimeric precursor [{RuCl(μ -Cl)(η^6 p-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 $[\operatorname{RuCl}_2(\eta^6 - p -$ Experimental Section). Compound cymene)(PPh₂Cl)] (2a) was previously described in the literature.¹⁸ Following the same approach, complex [RuCl₂(η^6 p-cymene)(PPhCl₂)] (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 $\binom{^{31}P}{^{1}H}$, ^{1}H , $^{13}C\binom{^{1}H}{^{3}}$ and $^{19}F\binom{^{1}H}{^{1}}$, 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 $^{^{31}P}\binom{^{1}H}{^{1}H}$ NMR spectra, the opposite trend was found for [RuCl₂(η^6 -p-cymene)(PPhCl₂)] (**3**) ($\delta_P = 145.6$ ppm vs 165.0 ppm for free PPhCl₂). The stronger π -accepting nature of

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

In addition, the structure of complex $[RuCl_2(\eta^{\circ}-p$ cymene)(PCy₂Cl)] (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 PCy₂Cl. 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 [RuCl₂(η^6 -benzene)(PCy₂Cl)] (Ru-P = 2.3247(4) Å).²⁰ As observed for $[RuCl_2(\eta^6-benzene)(PCy_2Cl)]$, the chlorine atom of the PCy₂Cl 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-Cl1 123.6(1), Ru-P1-Cl7 116.4(1), Cl1-P1-Cl3 97.5(1), Cl1-P1-Cl7 103.6(2), Cl7-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 CD₂Cl₂ 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)(PR₂Cl)] (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 [RuCl₂(η^6 -p-cymene)(PR₂OH)] derivatives (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 ³¹P{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 - $Cl(\eta^{\circ}-p-cymene)$ ₂] (1) with 2.2 equivalents Apple other corresponding secondary phosphine oxide R1P(=0)(F5(Scheme 5). We must note in this point that formation of $[RuCl_2(\eta^6-p$ cymene)(PPh₂OH)] (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 [RuCl₂(η^6 *p*-cymene)(PCy₂Cl)] (**2g**) and [RuCl₂(η^6 -*p*-cymene)(PPhCl₂)] (**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 ³¹P{¹H} NMR spectra at $\delta_{\rm P}$ 50 and 20 ppm corresponding to Cy₂P(=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 Cy₂POH and PhP(OH)₂ may be associated with the higher thermodynamic stability of their pentavalent tautomers Cy₂P(=O)H and PhP(=O)H(OH).



heme 5 Synthesis of the arene-ruthenium(II) complexes 4a-f,h. The novel phosphinous acid complexes [RuCl₂(η^6 -p-

cymene)(PR₂OH)] (R = $4 - C_6 H_4 F$ (4b), $4 - C_6 H_4 CF_3$ (4c), $4 - C_6 H_4 Me$ (4d), 4-C₆H₄OMe (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 [RuCl₂(η^6 -*p*-cymene)(PCy₂Cl)] (**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

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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-C1 2.388(2), Ru-C12 2.424(2), Ru-C¹ 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), Cl1-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)
comple	exes	s [RuCl	<u>a</u> (η ⁶ -p-cyme	ne)(PR ₂ Cl)] (2	a-h)	and	[RuCl₂(η ⁶ -p-
cymen	e)(F	PhCl ₂)] (3)	a					

	Ph-	<u>2 m</u> H ₂	ol% of Ru O / 80 °C Pl		
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 Departient ware performed under Ar atmosphere starting from 1 mmal of					

^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 $[RuCl_2(\eta^6-p-cymene){P(2-furyl)_2Cl}]$ (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 \geq 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/Cwith21the decoordination of P(2-furyl)₂OH since complex [RuCl₂(η^{6} -pcymene){P(2-furyl)₂OH}] (4f) was found to be perfectly stable in solution. The presence of the potentially coordinating 2furyl 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 [RuCl₂(η^6 -p-cymene)(PR₂OH)] are the active species in the hydration process, two antagonistic effects come into play: (i) the formation of $[RuCl_2(\eta^6-p$ cymene)(PR₂OH)] by hydrolysis of [RuCl₂(η^6 -p-cymene)(PR₂Cl)], 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 [RuCl₂(η° -p-cymene){P(4-C₆H₄F)₂Cl}] (**2b**) emerged as the most active, being able to generate benzamide in 98% GCyield after only 30 min (entry 2; > 99% after 1 h).^{23b} Remarkably, the in-situ-generated precatalyst, obtained by mixing the dimeric precursor [{RuCl(μ -Cl)(η^6 -p-cymene)}] (1) (1 mol%) with $P(4-C_6H_4F)_2Cl$ (2 mol%), presents the same

(1 mol%) with P(4-C₆H₄F)₂Cl (2 mol%), presents the same catalytic performance than that of the isolated complex [RuCl₂(η^6 -*p*-cymene){P(4-C₆H₄F)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 [RuCl₂(η^6 -p-cymene){P(4-C₆H₄F)₂Cl}] (**2b**): Effect of the metal loading and temperature^{*a*}

	Ph = N	2b (1-2 mol%) H ₂ O / r.t80 ℃	Ph NH ₂	
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 [RuCl₂(η^6 -p-cymene){P(4-C₆H₄F)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 (\geq 89% by GC; \geq 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 $[RuCl_2(\eta^6-p-cymene){P(4-C_6H_4F)_2Cl}] (2b)^{a}$

	R		
Entry	Nitrile	t (h)	Yield (%) ^b
1	R = Ph	4	> 99 (93)
2	$R = 2 - C_6 H_4 F$	5	> 99 (93)
3	$R = 4 - C_6 H_4 F$	2	> 99 (79)
4	$R = C_6 F_5$	10	92 (85)
5	$R = 3 - C_6 H_4 C I$	1.5	> 99 (89)
6	$R = 4 - C_6 H_4 C I$	9.5	98 (83)
7	$R = 2 - C_6 H_4 Br$	8	97 (78)
8	$R = 4 - C_6 H_4 Br$	5.5	98 (91)
9	$R = 4 - C_6 H_4 C(=O) Me$	3.5	96 (80)
10	$R = 4 - C_6 H_4 C (= O) H$	3.5	99 (77)
11	$R = 4 - C_6 H_4 C(=O)OEt$	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	$R = CH_2CI$	1	99 (93)
18	$R = CH_2OPh$	2	> 99 (96)
10	$R = CH_2$ -2-thienyl	2	> 99 (92)
20 ^c	$R = n - C_6 H_{13}$	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 lactams²⁷_{New Article Oming}²⁸ oxocyclohexenes,²⁹ isoquinolines,³⁰ Dopyrrologuinolines,²⁴ 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 -acylketenes³⁸ 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 Nunsubstituted 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

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Table 4 Catalytic hydration of β -ketonitriles using the ruthenium(II) compl	ex
$[\operatorname{RuCl}_2(\eta^6 - p - \operatorname{cymene}) \{ P(4 - C_6 H_4 F)_2 Cl \}] (\mathbf{2b})^{\alpha}$	

R	N 2b (2 mol%) H ₂ O / 40-80 °C /	0 14 h R		
Entry	eta-Ketonitrile	Temp. (°C)	Yield (%) ^b	K/E ratio ^{c}
1	R = Ph	40	77	1.6:1
2	$R = 4 - C_6 H_4 F$	40	88	2.2:1
3	$R = 2 - C_6 H_4 C I$	40	75	1:1.8
4	$R = 3 - C_6 H_4 C I$	40	80	1.1:1
5	$R = 4 - C_6 H_4 C I$	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	$R = 4 - C_6 H_4 Me$	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 ¹H 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 ³¹P{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 [RuCl₂(η^6 -p-cymene){P(4-C₆H₄F)₂Cl}] (2b) is completely converted into the active compound [RuCl₂(η^6 -p-cymene){P(4-C₆H₄F)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-C₆H₄F)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 PR2OH, which are wellknown "cooperative" ligands for this catalytic transformation. In particular, using the arene-ruthenium(II) complex [RuCl₂(η^{6} p-cymene){P(4-C₆H₄F)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

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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)}] (**1**)⁴⁸ and [RuCl₂(η^6 -pcymene)(PPh₂OH)] (**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 ¹³C), to an external 85% aqueous H_3PO_4 solution (³¹P), or to the CFCl₃ standard (¹⁹F). DEPT experiments have been carried out for all the compounds reported.

Synthesis of $[RuCl_2(\eta^6-p-cymene)(PR_2Cl)]$ (R = Ph (20), $4C_6H_4E$ (2b), $4-C_6H_4CF_3$ (2c), $4-C_6H_4Me$ (2d), $4-C_6H_4OMe_3(2e)$, 2: furzyl (2f), Cy (2g), Et (2h))

A suspension of the dimeric precursor [{RuCl(μ -Cl)(η^6 -p-(15 mL) 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 orangered solid residue washed with hexanes (3 x 20 mL), and dried in vacuo. (2a):¹⁸ Yield: 0.230 g (81%). ${}^{31}P{}^{1}H{}$ NMR (CD₂Cl₂): $\delta =$ 96.6 (s) ppm. ¹H NMR (CD₂Cl₂): 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, ${}^{3}J_{HH} = 6.0$ Hz, CHMe₂), 2.02 (s, 3H, Me), 1.21 (d, 6H, ${}^{3}J_{HH} = 6.0$ Hz, CHMe₂) ppm. ¹³C{¹H} NMR (CD₂Cl₂): 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, ${}^{2}J_{PC}$ = 5.0 Hz, CH of cym), 88.3 (d, ²J_{PC} = 6.0 Hz, CH of cym), 30.5 (s, CHMe₂), 21.7 (s, CHMe₂), 17.6 (s, Me) ppm. Elemental analysis calcd. (%) for C₂₂H₂₄Cl₃PRu: C 50.16, H 4.59; found: C 50.27, H 4.69. (2b): Yield: 0.264 g (87%). ${}^{31}P{}^{1}H{} NMR (CD_{2}Cl_{2}): \delta = 94.4$ (s) ppm. ${}^{1}H{}$ NMR (CD₂Cl₂): δ = 7.93 and 7.19 (m, 4H each, C₆H₄F), 5.43 and 5.36 (d, 2H each, ${}^{3}J_{HH}$ = 6.0 Hz, CH of cym), 2.86 (sept, 1H, ${}^{3}J_{HH}$ = 6.9 Hz, CHMe₂), 2.03 (s, 3H, Me), 1.22 (d, 6H, ³J_{HH} = 6.9 Hz, CH Me_2) ppm. ¹³C{¹H} NMR (CD₂Cl₂): δ = 164.0 (dd, ¹ J_{FC} = 253.4 Hz, ${}^{4}J_{PC}$ = 2.5 Hz, C of C₆H₄F), 135.5 (dd, ${}^{2}J_{PC}$ = 13.4 Hz, ${}^{3}J_{FC}$ = 8.8 Hz, CH of C_6H_4F), 131.2 (dd, ${}^{1}J_{PC}$ = 39.3 Hz, ${}^{4}J_{FC}$ = 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, ${}^{2}J_{PC}$ = 6.4 Hz, CH of cym), 30.6 (s, CHMe₂), 21.6 (s, CHMe₂), 17.6 (s, Me) ppm. ${}^{19}F{}^{1}H{}$ NMR (CD₂Cl₂): δ = -108.2 (d, ${}^{4}J_{PF}$ = 2.3 Hz) ppm. Elemental analysis calcd. (%) for C₂₂H₂₂Cl₃F₂PRu: C 46.95, H 3.94; found: C 46.82, H 4.02. (2c): Yield: 0.207 g (58%). ${}^{31}P{}^{1}H{}$ NMR (CD₂Cl₂): δ = 93.5 (s) ppm. ${}^{1}H{}$ NMR (CD₂Cl₂): δ = 8.09 (dd, 4H, ${}^{3}J_{PH}$ = 10.5 Hz, ${}^{3}J_{HH}$ = 8.6 Hz, $C_{6}H_{4}CF_{3}$), 7.70 (dd, 4H, ${}^{3}J_{HH}$ = 8.6 Hz, ${}^{4}J_{PH}$ = 1.8 Hz, $C_{6}H_{4}CF_{3}$), 5.50 and 5.42 (d, 2H each, ${}^{3}J_{HH}$ = 6.1 Hz, CH of cym), 2.87 (sept, 1H, ${}^{3}J_{HH}$ = 6.9 Hz, CHMe₂), 2.06 (s, 3H, Me), 1.23 (d, 6H, ${}^{3}J_{HH}$ = 6.9 Hz, CHMe₂) ppm. ¹³C{¹H} NMR (CD₂Cl₂): 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, ${}^{2}J_{FC}$ = 32.7 Hz, C of C₆H₄CF₃), 124.8 (dq, ${}^{3}J_{PC}$ = 10.8 Hz, ${}^{3}J_{FC}$ = 3.7 Hz, CH of C₆H₄CF₃), 123.5 (q, ${}^{1}J_{FC}$ = 272.5 Hz, CF₃), 111.6 and 99.5 (s, C of cym), 91.3 (d, ${}^{2}J_{PC}$ = 4.4 Hz, CH of cym), 88.7 (d, ²J_{PC} = 6.0 Hz, CH of cym), 30.6 (s, CHMe₂), 21.6 (s, CH*Me*₂), 17.7 (s, Me) ppm. ¹⁹F{¹H} NMR (CD₂Cl₂): 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%). ${}^{31}P{}^{1}H{}$ NMR (CD₂Cl₂): δ = 97.3 (s) ppm. ${}^{1}H{}$ NMR (CD_2CI_2) : δ = 7.78 (dd, 4H, ${}^{3}J_{PH}$ = 11.4 Hz, ${}^{3}J_{HH}$ = 8.3 Hz, C_6H_4 Me), 7.25 (dd, 4H, ${}^{3}J_{HH}$ = 8.3 Hz, ${}^{4}J_{PH}$ = 2.4 Hz, C₆H₄Me), 5.39 and 5.34 (d, 2H each, ${}^{3}J_{HH}$ = 6.3 Hz, CH of cym), 2.84 (sept, 1H, ${}^{3}J_{HH}$ = 6.9 Hz, CHMe₂), 2.41 (s, 6H, C₆H₄Me), 2.02 (s, 3H, Me), 1.21 (d, 6H, ${}^{3}J_{HH}$ = 6.9 Hz, CHMe₂) ppm. ${}^{13}C{}^{1}H{}$ NMR (CD₂Cl₂): 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, ${}^{1}J_{PC}$ = 38.2 Hz, C of C₆H₄Me), 128.5 (d, J_{PC} = 11.0 Hz, CH of C₆H₄Me), 110.6 and 98.2 (s, C of cym), 91.5 (d, ${}^{2}J_{PC}$ = 4.4 Hz, CH of cym), 88.2 (d, ${}^{2}J_{PC}$ = 6.2 Hz, CH of cym), 30.5 (s,

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CHMe₂), 21.7 (s, CHMe₂), 21.2 (s, C₆H₄Me), 17.6 (s, Me) ppm. Elemental analysis calcd. (%) for C₂₄H₂₈Cl₃PRu: C 51.95, H 5.09; found: C 51.80, H 5.22. (2e): Yield: 0.310 g (98%). ³¹P{¹H} NMR (CD₂Cl₂): δ = 96.6 (s) ppm. ¹H NMR (CD₂Cl₂): δ = 7.86-7.79 (m, 4H, C_6H_4 OMe), 6.94 (dd, 4H, ${}^3J_{HH} = 9.0$ Hz, ${}^4J_{PH} = 1.4$ Hz, C_6H_4 OMe), 5.39 and 5.33 (d, 2H each, ${}^{3}J_{HH} = 6.3$ Hz, CH of cym), 3.87 (s, 6H, OMe), 2.85 (sept, 1H, ³J_{HH} = 6.9 Hz, CHMe₂), 2.02 (s, 3H, Me), 1.22 (d, 6H, ${}^{3}J_{HH} = 6.9$ Hz, CHMe₂) ppm. ${}^{13}C{}^{1}H{}$ NMR (CD₂Cl₂): δ = 162.0 (s, C of C₆H₄OMe), 134.8 (d, J_{PC} = 13.3 Hz, CH of C₆H₄OMe), 126.9 (d, ${}^{1}J_{PC}$ = 41.9 Hz, C of C₆H₄OMe), 113.2 (d, J_{PC} = 11.9 Hz, CH of C₆H₄OMe), 110.6 and 98.0 (s, C of cym), 91.4 (d, ${}^{2}J_{PC}$ = 4.4 Hz, CH of cym), 88.1 (d, ${}^{2}J_{PC}$ = 6.2 Hz, CH of cym), 55.4 (s, OMe), 30.5 (s, CHMe₂), 21.6 (s, CHMe₂), 17.6 (s, Me) ppm. Elemental analysis calcd. (%) for C₂₄H₂₈Cl₃O₂PRu: C 49.12, H 4.81; found: C 49.27, H 4.82. (2f): Yield: 0.235 g (86%). ${}^{31}P{}^{1}H{}$ NMR (CD₂Cl₂): δ = 55.6 (s) ppm. ${}^{1}H{}$ NMR (CD₂Cl₂): 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, ${}^{3}J_{HH} = 6.0$ Hz, CH of cym), 2.84 (sept, 1H, ${}^{3}J_{HH} = 7.1$ Hz, $CHMe_2$), 2.08 (s, 3H, Me), 1.18 (d, 6H, ${}^{3}J_{HH}$ = 7.1 Hz, $CHMe_2$) ppm. ¹³C{¹H} NMR (CD₂Cl₂): δ = 148.3 (d, ³J_{PC} = 6.3 Hz, CH of furyl), 145.9 (d, ${}^{1}J_{PC}$ = 65.6 Hz, C of furyl), 125.1 (d, ${}^{2}J_{PC}$ = 19.1 Hz, CH of furyl), 111.5 (d, ${}^{3}J_{PC}$ = 7.3 Hz, CH of furyl), 111.0 and 99.1 (s, C of cym), 91.8 (d, ${}^{2}J_{PC}$ = 5.8 Hz, CH of cym), 88.2 (d, ${}^{2}J_{PC}$ = 7.0 Hz, CH of cym), 30.5 (s, CHMe₂), 21.4 (s, CHMe₂), 17.6 (s, Me) ppm. Elemental analysis calcd. (%) for C₁₈H₂₀Cl₃O₂PRu: C 42.66, H 3.98; found: C 42.80, H 4.16. (2g): Yield: 0.227 g (78%). ${}^{31}P{}^{1}H{}$ NMR (CD₂Cl₂): δ = 155.7 (s) ppm. ${}^{1}H{}$ NMR (CD_2Cl_2) : δ = 5.47 (br, 4H, CH of cym), 2.97 (sept, 1H, ${}^{3}J_{HH}$ = 7.5 Hz, CHMe₂), 2.80-2.60 (m, 2H, CH of Cy), 2.14 (s, 3H, Me), 1.90-1.60 (m, 14H, CH₂), 1.30-1.26 (m, 6H, CH₂), 1.26 (d, 6H, ${}^{3}J_{HH} =$ 7.5 Hz, CHMe₂) ppm. ${}^{13}C{}^{1}H{}$ NMR (CD₂Cl₂): δ = 106.6 and 98.5 (s, C of cym), 90.6 (d, ${}^{2}J_{PC}$ = 5.0 Hz, CH of cym), 89.5 (d, ${}^{2}J_{PC}$ = 4.0 Hz, CH of cym), 40.7 (d, ${}^{2}J_{PC}$ = 9.0 Hz, CH of Cy), 29.9 (s, CHMe₂), 27.1 and 25.8 (s, CH₂), 26.6 (d, J_{PC} = 13.0 Hz, CH₂), 26.5 (d, J_{PC} = 11.0 Hz, CH₂), 25.9 (d, J_{PC} = 3.0 Hz, CH₂), 21.7 (s, CHMe2), 17.5 (s, Me) ppm. Elemental analysis calcd. (%) for C₂₂H₃₆Cl₃PRu: C 49.03, H 6.73; found: C 48.93, H 6.90. (2h): Yield: 0.188 g (81%). ${}^{31}P{}^{1}H{}$ NMR (CD₂Cl₂): δ = 135.7 (s) ppm. ¹H NMR (CD₂Cl₂): 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, CHMe₂), 2.62-2.32 (m, 4H, CH₂), 2.14 (s, 3H, Me), 1.25 (d, 6H, ³J_{HH} = 6.9 Hz, CH*Me*₂), 1.23 (dt, ${}^{3}J_{PH}$ = 18.0 Hz, ${}^{3}J_{HH}$ = 7.5 Hz, CH₂CH₃) ppm. ${}^{13}C{}^{1}H$ NMR (CD₂Cl₂): δ = 108.1 and 97.6 (s, C of cym), 90.1 (d, ²J_{PC} = 5.1 Hz, CH of cym), 87.8 (d, ${}^{2}J_{PC}$ = 5.7 Hz, CH of cym), 30.4 (s, CHMe₂), 25.5 (d, ¹J_{PC} = 18.2 Hz, CH₂), 21.7 (s, CHMe₂), 17.8 (s, Me), 7.8 (d, ${}^{2}J_{PC}$ = 5.0 Hz, CH₂CH₃) ppm. Elemental analysis calcd. (%) for C₁₄H₂₄Cl₃PRu: C 39.04, H 5.62; found: C 39.15, H 5.74.

Synthesis of $[RuCl_2(\eta^6-p-cymene)(PPhCl_2)]$ (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

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with diethyl ether (3 x 20 mL), and dried in vacuovi Vield: 0.196 g (75%). ³¹P{¹H} NMR (CD₂Cl₂): δ = 145.6¹(5).1970.5⁵H⁰NMR (CD₂Cl₂): δ = 8.13-7.51 (m, 5H, Ph), 5.36 (br, 4H, CH of cym), 2.89 (sept, 1H, ³J_{HH} = 6.0 Hz, CHMe₂), 2.13 (s, 3H, Me), 1.25 (d, 6H, ³J_{HH} = 6.0 Hz, CHMe₂) ppm. ¹³C{¹H} NMR (CD₂Cl₂): 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), 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, CHMe₂), 21.5 (s, CHMe₂), 17.8 (s, Me) ppm. Elemental analysis calcd. (%) for C₁₆H₁₉Cl₄PRu: C 39.61, H 3.95; found: C 39.51, H 4.08.

Synthesis of $[RuCl_2(\eta^6-p-cymene)(PR_2OH)]$ (R = 4-C₆H₄F (4b), 4-C₆H₄CF₃ (4c), 4-C₆H₄Me (4d), 4-C₆H₄OMe (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 R₂P(=O)H, generated in situ by reacting the corresponding chlorophosphine PR₂Cl (0.59 mmol) with H₂O (17 μ L, 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 orangered 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_2Cl_2 as the eluent. **(4b)**: Yield: 0.250 g (85%). IR (KBr): v = 3145 (w, O-H) cm⁻¹. ³¹P{¹H} NMR (CD₂Cl₂): $\delta =$ 106.1 (s) ppm. ¹H NMR (CD₂Cl₂): δ = 7.70 and 7.23 (m, 4H each, C_6H_4F), 5.40 and 5.30 (d, 2H each, ${}^{3}J_{HH}$ = 5.7 Hz, CH of cym), 2.53 (sept, 1H, ³J_{HH} = 6.9 Hz, CHMe₂), 2.01 (s, 3H, Me), 1.03 (d, 6H, ${}^{3}J_{HH} = 6.9$ Hz, CHMe₂) ppm; OH signal not observed. ${}^{13}C{}^{1}H{}$ NMR (CD₂Cl₂): δ = 164.5 (d, ¹J_{FC} = 250.3 Hz, C of C₆H₄F), 133.9 (dd, ${}^{2}J_{PC}$ = 13.1 Hz, ${}^{3}J_{FC}$ = 8.6 Hz, CH of C₆H₄F), 133.2 (d, ${}^{1}J_{PC}$ = 62.6 Hz, C of C₆H₄F), 115.6 (dd, ${}^{2}J_{FC}$ = 21.4 Hz, ${}^{3}J_{PC}$ = 11.8 Hz, CH of C₆H₄F), 109.0 and 97.3 (s, C of cym), 89.3 (d, ${}^{2}J_{PC}$ = 4.5 Hz, CH of cym), 87.1 (d, ${}^{2}J_{PC}$ = 5.4 Hz, CH of cym), 30.4 (s, CHMe₂), 21.5 (s, CH*Me*₂), 17.6 (s, Me) ppm. ${}^{19}F{}^{1}H{}$ NMR (CD₂Cl₂): δ = -108.6 (d, ${}^{4}J_{PF}$ = 2.0 Hz) ppm. Elemental analysis calcd. (%) for C₂₂H₂₃Cl₂F₂OPRu: C 48.54, H 4.26; found: C 48.40, H 4.11. (4c): Yield: 0.181 g (52%). IR (KBr): v = 3185 (w, O-H) cm⁻¹. ³¹P{¹H} NMR (CD₂Cl₂): δ = 105.9 (s) ppm. ¹H NMR (CD₂Cl₂): δ = 7.88-7.79 (m, 8H, $C_6H_4CF_3$), 5.46 and 5.32 (d, 2H each, ${}^3J_{HH}$ = 5.8 Hz, CH of cym), 2.50 (sept, 1H, ${}^{3}J_{HH} = 6.9$ Hz, CHMe₂), 2.05 (s, 3H, Me), 1.02 (d, 6H, ${}^{3}J_{HH}$ = 6.9 Hz, CH*Me*₂) ppm; OH signal not observed. ¹³C{¹H} NMR (CD₂Cl₂): δ = 141.2 (d, ¹J_{PC} = 54.6 Hz, C of C₆H₄CF₃), 132.8 (q, ${}^{2}J_{FC}$ = 31.6 Hz, C of C₆H₄CF₃), 131.8 (d, ${}^{2}J_{PC}$ = 12.0 Hz, CH of C₆H₄CF₃), 125.3 (dq, ${}^{3}J_{PC}$ = 10.8 Hz, ${}^{3}J_{FC}$ = 3.7 Hz, CH of $C_6H_4CF_3$), 123.7 (q, ${}^{1}J_{FC}$ = 272.9 Hz, CF_3), 109.2 and 98.0 (s, C of cym), 89.4 (d, ${}^{2}J_{PC}$ = 4.6 Hz, CH of cym), 87.5 (d, ${}^{2}J_{PC}$ = 5.3 Hz, CH of cym), 30.5 (s, CHMe₂), 21.4 (s, CHMe₂), 17.7 (s, Me) ppm. ¹⁹F{¹H} NMR (CD₂Cl₂): δ = -63.4 (s) ppm. Elemental analysis calcd. (%) for C₂₄H₂₃F₆Cl₂OPRu: C 44.74, H 3.60; found: C 44.63, H 3.53. (4d): Yield: 0.165 g (57%). IR (KBr): v =

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3037 (w, O-H) cm⁻¹. ³¹P{¹H} NMR (CD₂Cl₂): δ = 106.8 (s) ppm. ¹H NMR (CD₂Cl₂): δ = 7.58 (dd, 4H, ³J_{PH} = 10.8 Hz, ³J_{HH} = 8.0 Hz, C_6H_4Me), 7.33 (dd, 4H, ${}^{3}J_{HH}$ = 8.0 Hz, ${}^{4}J_{PH}$ = 1.8 Hz, C_6H_4Me), 5.38 and 5.27 (d, 2H each, ${}^{3}J_{HH} = 5.6$ Hz, CH of cym), 2.50 (sept, 1H, ${}^{3}J_{HH} = 6.9$ Hz, CHMe₂), 2.45 (s, 6H, C₆H₄Me), 1.99 (s, 3H, Me), 1.02 (d, 6H, ${}^{3}J_{HH}$ = 6.9 Hz, CHMe₂) ppm; OH signal not observed. ¹³C{¹H} NMR (CD₂Cl₂): δ = 141.6 (d, ⁴J_{PC} = 2.3 Hz, C of C_6H_4Me), 134.3 (d, ${}^{1}J_{PC}$ = 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, ${}^{2}J_{PC}$ = 5.0 Hz, CH of cym), 86.8 (d, ${}^{2}J_{PC}$ = 5.8 Hz, CH of cym), 30.6 (s, CHMe₂), 21.5 (s, CHMe₂), 21.2 (s, C₆H₄Me), 17.5 (s, Me) ppm. Elemental analysis calcd. (%) for C₂₄H₂₉Cl₂OPRu: C 53.74, H 5.45; found: C 53.61, H 5.50. (4e): Yield: 0.301 g (98%). IR (KBr): v = 3196 (w, O-H) cm^{-1} . ³¹P{¹H} NMR (CD₂Cl₂): δ = 105.9 (s) ppm. ¹H NMR (CD₂Cl₂): δ = 7.63 (dd, 4H, ${}^{3}J_{PH}$ = 10.2 Hz, ${}^{3}J_{HH}$ = 8.0 Hz, C₆H₄OMe), 7.03 (dd, 4H, ${}^{3}J_{HH}$ = 8.6 Hz, ${}^{4}J_{PH}$ = 1.5 Hz, C₆H₄OMe), 5.38 and 5.28 (d, 2H each, ${}^{3}J_{HH} = 5.7$ Hz, CH of cym), 3.89 (s, 6H, OMe), 2.55 (sept, 1H, ³J_{HH} = 6.9 Hz, CHMe₂), 1.99 (s, 3H, Me), 1.03 (d, 6H, ${}^{3}J_{HH} = 6.9$ Hz, CHMe₂) ppm; OH signal not observed. ${}^{13}C{}^{1}H{}$ NMR (CD₂Cl₂): δ = 161.9 (s, C of C₆H₄OMe), 133.5 (d, J_{PC} = 13.0 Hz, CH of C₆H₄OMe), 128.9 (d, ${}^{1}J_{PC}$ = 62.9 Hz, C of C₆H₄OMe), 113.6 (d, J_{PC} = 11.7 Hz, CH of C₆H₄OMe), 108.4 and 96.4 (s, C of cym), 89.3 (d, ${}^{2}J_{PC}$ = 4.6 Hz, CH of cym), 86.8 (d, ${}^{2}J_{PC}$ = 5.6 Hz, CH of cym), 55.5 (s, OMe), 30.4 (s, CHMe₂), 21.5 (s, CHMe₂), 17.6 (s, Me) ppm. Elemental analysis calcd. (%) for C₂₄H₂₉O₃Cl₂PRu: C 50.71, H 5.14; found: C 50.56, H 5.12. (4f): Yield: 0.224 g (85%). IR (KBr): v = 3125 (w, O-H) cm⁻¹. ³¹P{¹H} NMR (CD₂Cl₂): δ = 78.1 (s) ppm. ¹H NMR (CD₂Cl₂): δ = 7.70 (br, 2H, CH of furyl), 7.05 (d, 2H, ${}^{3}J_{HH}$ = 3.0 Hz, CH of furyl), 6.63 (br, 2H, CH of furyl), 5.57 (br, 4H, CH of cym), 2.65 (sept, 1H, ${}^{3}J_{HH} =$ 6.9 Hz, CHMe₂), 2.03 (s, 3H, Me), 1.10 (d, 6H, ³J_{HH} = 7.1 Hz, CHMe₂) ppm; OH signal not observed. ¹³C{¹H} NMR (CD₂Cl₂): δ = 150.0 (d, ${}^{1}J_{PC}$ = 90.3 Hz, C of furyl), 147.6 (d, ${}^{3}J_{PC}$ = 6.7 Hz, CH of furyl), 121.4 (d, ${}^{2}J_{PC}$ = 15.9 Hz, CH of furyl), 111.2 (d, ${}^{3}J_{PC}$ = 6.7 Hz, CH of furyl), 108.7 and 97.3 (s, C of cym), 90.1 (d, ${}^{2}J_{PC}$ = 5.4 Hz, CH of cym), 86.9 (d, ${}^{2}J_{PC}$ = 6.3 Hz, CH of cym), 30.6 (s, CHMe₂), 21.4 (s, CHMe₂), 17.8 (s, Me) ppm. Elemental analysis calcd. (%) for C₁₈H₂₁O₃Cl₂PRu: C 44.28, H 4.33; found: C 44.37, H 4.45. (4h): Yield: 0.129 g (58%). IR (KBr): v = 3180 (w, O-H) cm^{-1} . ³¹P{¹H} NMR (CD₂Cl₂): δ = 126.6 (s) ppm. ¹H NMR (CD₂Cl₂): δ = 5.54 and 5.50 (d, 2H each, ${}^{3}J_{HH}$ = 5.8 Hz, CH of cym), 2.76 (sept, 1H, ³J_{HH} = 7.2 Hz, CHMe₂), 2.28-2.21 (m, 4H, CH₂), 2.09 (s, 3H, Me), 1.26 (d, 6H, ³J_{HH} = 7.2 Hz, CH*Me*₂), 1.23 (dt, ³J_{PH} = 16.2 Hz, ${}^{3}J_{HH} = 7.6$ Hz, CH₂CH₃) ppm; OH signal not observed. ${}^{13}C{}^{1}H{}$ NMR (CD₂Cl₂): δ = 106.8 and 95.0 (s, C of cym), 89.2 (d, ²J_{PC} = 4.5 Hz, CH of cym), 85.6 (d, ${}^{2}J_{PC}$ = 5.4 Hz, CH of cym), 30.8 (s, CHMe₂), 25.2 (d, ¹J_{PC} = 33.9 Hz, CH₂), 21.8 (s, CHMe₂), 18.1 (s, Me), 6.7 (d, ${}^{2}J_{PC}$ = 3.7 Hz, CH₂CH₃) ppm. Elemental analysis calcd. (%) for C₁₄H₂₅Cl₂OPRu: C 40.78, H 6.11; found: C 40.61, H 6.27.

General procedure for the catalytic hydration of nitriles with $[RuCl_2(\eta^6\text{-}p\text{-}cymene)\{P(4\text{-}C_6H_4F)_2Cl\}]$ (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 μ L, which, after extraction with CH₂Cl₂ (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 [RuCl₂(η^6 -p-cymene){P(4-C₆H₄F)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-K α 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 H10 (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 $\sigma(F_0^2)$ from counting statistics and $P = [Max (F_o^2, 0) + 2F_c^2]/3$. Atomic scattering factors were taken from International Tables for Xray 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 ₃ PRu	C ₂₄ H ₂₃ F ₆ Cl ₂ OPRu		
Formula weight	538.90	644.36		
Temperature/K	293(2)	293(2)		
Wavelength/Å	1.54184	1.54184		
Crystal system	Triclinic	Monoclinic		
Space group	<i>P</i> -1	P21/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		
Ζ	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 ≤ <i>h</i> ≤ 9	$-5 \le h \le 8$		
	-12 ≤ <i>k</i> ≤ 9	-13 ≤ <i>k</i> ≤ 13		
	-17 ≤ / ≤ 18	-40 ≤ <i>l</i> ≤ 40		
Completeness to $artheta_{max}$	97.5%	99.3%		
No. of refins. collected	9679	21368		
No. of unique reflns.	4410 (<i>R</i> _{int} = 0.040)	4804 (R _{int} = 0.038)		
No. of parameters/restraints	244/0	317/0		
Refinement method	Full-matrix leas	t-squares on <i>F</i> ²		
Goodness-of-fit on F ²	1.060	1.170		
Weight function (a, b)	0.0480, 0.0973	0.0203, 12.0241		
$R_1 \left[l > 2\sigma(l) \right]^{\sigma}$	0.0335	0.0528		
$wR_2 \left[l > 2\sigma(l) \right]^a$	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 $R_{1} = \sum (E - E) / \sum E \cdot w R_{2} = \{\sum w (E^{2} - E^{2})^{2} \} / \sum w (E^{2} - 2)^{2} \}^{1/2}$				

 ${}^{a}R_{1} = \sum (|F_{o}| - |F_{c}|) / \sum |F_{o}|; wR_{2} = \{\sum [w(F_{o}^{2} - F_{c}^{2})^{2}] / \sum [w(F_{o}^{2})^{2}] \}^{1/2}$

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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.

