# Green Chemistry

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View Article Online
DOI: 10.1039/C3GC41201F



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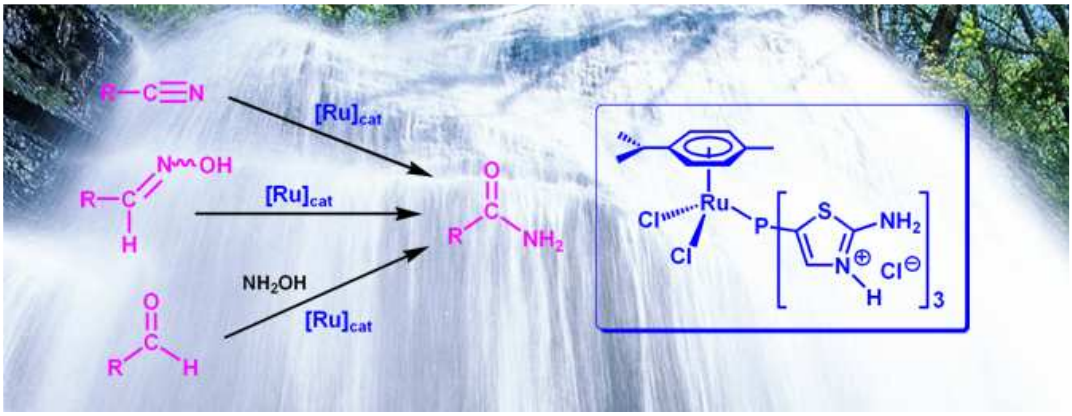
The preparation of new water-soluble ligands, consisting of *N*-protonated thiazolyl-phosphine salts, and their coordination to the ruthenium(II) fragment [$RuCl_2(\eta^6$-*p*-cymene)] is presented. The resulting complexes showed an outstanding activity in the selective hydration of organonitriles to primary amides, and related amide bond forming reactions, in environmentally friendly aqueous medium, allowing fast conversions, a facile product separation and catalyst recycling.



Cite this: DOI: 10.1039/c0xx00000x

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View Article Online
DOI: 10.1039/C3GC41201F

ARTICLE TYPE

# Thiazolyl-phosphine hydrochloride salts: Effective auxiliary ligands for ruthenium-catalyzed nitrile hydration reactions and related amide bond forming processes in water

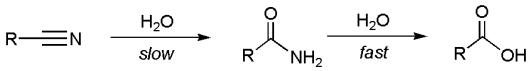
**Rocío García-Álvarez,[a] Maria Zablocka,*[b,c] Pascale Crochet,[a] Carine Duhayon,[b] Jean-Pierre Majoral,*[b] and Victorio Cadierno*[a]**

***Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X***
**DOI: 10.1039/b000000x**

A series of water-soluble *N*-protonated thiazolyl-phosphine hydrochloride salts have been synthesized and coordinated to the ruthenium(II) fragment [$RuCl_2(\eta^6$-*p*-cymene)]. The resulting complexes were evaluated as potential catalysts for the selective hydration of nitriles to primary amides in environmentally friendly aqueous medium. Best results in terms of activity were achieved when tris(5-(2-aminothiazolyl))phosphine trihydrochloride was used as ligand. Using the Ru(II) complex **9** derived from this salt (3 mol%), the catalytic reactions proceeded cleanly in pure water at 100 ºC without the assistance of any additive, affording the desired amides in high yields (> 78%) after short reaction periods (0.5-7 h). The process was operative with both aromatic, heteroaromatic, *α,β*-unsaturated and aliphatic nitriles, and tolerated several functional groups. The utility of **9** to promote the formation of primary amides in water by catalytic rearrangement of aldoximes and direct coupling of aldehydes with $NH_2OH{\cdot}HCl$ has also been demonstrated.

## Introduction

Hydration of nitriles to the corresponding primary amides is an important transformation given the role of amides as key synthetic intermediates in the production of a large variety of pharmaceutical products, drugs stabilizers, engineering plastics, detergents and lubricants.[1,2,3] Conventional methods of hydrating nitriles with strong acid and base catalysts suffer of several drawbacks, such as low functional group tolerance, undesired hydrolysis of the amides into carboxylic acids (Scheme 1), and extensive formation of salts after the neutralization of the catalysts.[1,4]




**Scheme 1** The nitrile hydration and amide hydrolysis reactions.

Enzymatic catalysis offers cleaner and more selective protocols for the conversion of nitriles to amides, but, despite the advances reached in the field and its commercial success, the high cost and narrow susbtrate specificity of the presently available enzymes severely limit their use.[5,6] Given their greater substrate scope, methods based on homogeneous[7] or heterogeneous[8] metal-based catalysts represent more attractive and powerful alternatives. Concerning the homogeneous ones, complexes $[RuH_2(PPh_3)_4]$[9] and $[PtH(PMe_2OH)\{(PMe_2O)_2H\}]$,[10] developed by Murahashi´s and Parkin´s groups, represent prototypical examples of highly active and selective catalysts showing excellent functional group tolerance and applicability in the syntheses of complex organic molecules and natural products. The remarkable activity shown by the rhodium-based systems $[\{Rh(\mu\text{-OMe})(cod)\}_2]/PCy_3$ (cod = 1,5-cyclooctadiene)[11] and [RhBr(PIN)(cod)] (PIN = 1-isopropyl-3-(5,7-dimethyl-1,8-naphthyrid-2-yl)imidazol-2-ylidene)[12] under ambient conditions deserves to be also highlighted, although we must note that in the latter case a base ($KO^tBu$) was employed as co-catalyst.

Most of the known homogeneous catalysts for nitrile hydration, including the examples commented above, operate in organic media in the presence of only small amounts of water.[7] In the search of more environmentally benign and safer procedures, considerable efforts have been devoted in recent years to the development of transition-metal complexes able to hydrate nitriles directly in water. In addition to the current interest in this green reaction medium,[13] its use as solvent for this particular transformation is specially advantageous since water itself participates as reactant. Among the different systems discovered,[14] the most promising results have been obtained with the ruthenium complexes **A-F** depicted in Fig. 1.[15] All of them operate in pure water without the assistance of any acidic or basic additive, showing a wide substrate scope and high tolerance to common functional groups. The excellent efficiencies found were attributed to the presence of hydrophilic phosphine ligands in their structures, which not only facilitate the solubility of these catalysts in the medium, but also exert an activating effect on the water molecules by H-bonding. By this way, the key nucleophilic attack by water on the coordinated nitrile is favoured.

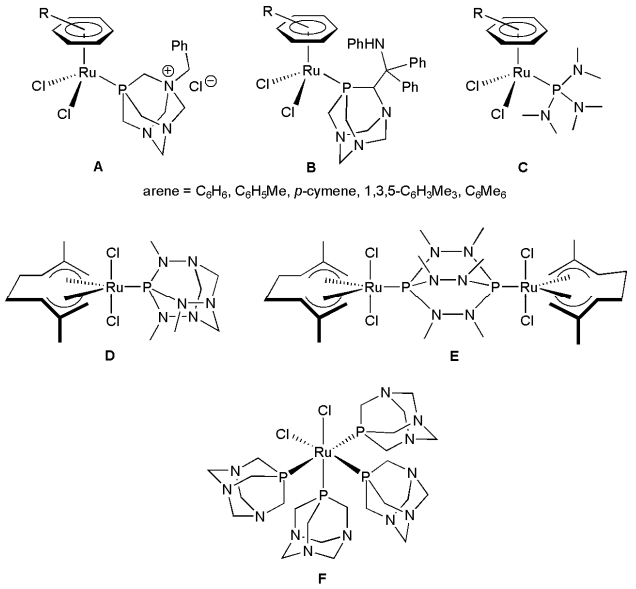
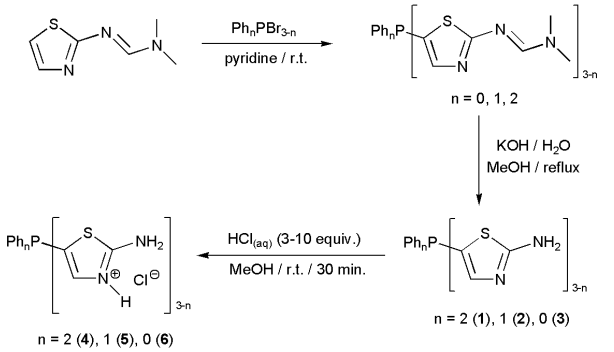



**Fig. 1** Ruthenium complexes active in the catalytic hydration of nitriles in water under neutral conditions.

The cooperative effect of the ancillary ligands in catalytic nitrile hydration reactions was first evidenced in organic media by Oshiki and Breit employing as catalysts ruthenium complexes containing pyridyl-phosphines.[16] In the search of new efficient systems active in water, we considered the development of related water-soluble heteroaryl-phosphines as alternatives to the most commonly used "cage-like" ones (structures **A-B** and **D-F** in Fig. 1). In our search, we have found that arene-ruthenium(II) complexes containing thiazolyl-phosphine hydrochloride salts are competitive alternatives to catalysts **A-F** for the efficient and selective conversion of nitriles to amides in water. The utility of these new water-soluble complexes is not restricted to the catalytic hydration of nitriles, since they proved also effective for the formation of primary amides in water by catalytic rearrangement of aldoximes and direct coupling of aldehydes with $NH_2OH{\cdot}HCl$. We must also indicate in this point that thiazolyl-phosphines represent an almost unexploited class of ancillary ligands for catalysis. Thus, to the best of our knowledge, this type of phosphines have only been previously involved in copper-catalyzed *N*-arylation reactions[17] and Suzuki-type cross-coupling processes.[18]

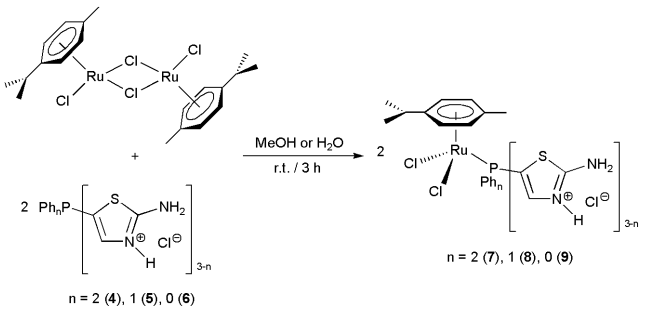
## Results and discussion

The hydrochloride salts **4-6** were readily synthesized in quantitative yield by treatment of methanolic solutions of the known 5-(2-aminothiazolyl)-phosphines **1-3**[17,19] with an excess of aqueous hydrochloric acid under mild conditions (Scheme 2). As expected, the selective protonation of the more basic iminic nitrogen atom of the 2-aminothiazolyl rings was in all the cases observed. The $^{31}P\{^1H\}$, $^1H$ and $^{13}C\{^1H\}$ NMR data obtained for these new compounds **4-6** are very similar to those previously reported for **1-3**, with a slight shielding of the C-4 carbon resonances of the thiazolyl rings ($\Delta\delta$ from -10 to -15 ppm) being the most noticiable difference. In addition, the structure of tris(5-(2-aminothiazolyl))phosphine trihydrochloride (**6**) was unequivocally confirmed by means of X-ray diffraction methods (an ORTEP plot and selected bonding parameters are included in the ESI file).‡ As expected, salts **4-6** are soluble in water, but their solubility profile was found to be strongly influenced by the number of thiazolium units linked to the phosphorus atom. Thus, while phosphine **4** containing only one thiazolium unit is only slightly soluble (6 g/L), the presence of two or three thiazolium moieties in **5** and **6** results in a considerable increase of the solubility (250 and 275 g/L, respectively).[20]




**Scheme 2** Synthesis of the thiazolyl-phosphine hydrochloride salts **4-6**.

Treatment of the ruthenium(II) dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$[21] with two equivalents of the hydrochloride salts **4-6**, in methanol (**4-5**) or water (**6**) at room temperature, results in the formation of bright red solutions from which the mononuclear derivatives **7-9** could be isolated, as air-stable solids in 78-85% yield, after partial removal of the solvent in vacuo and subsequent precipitation with pentane (Scheme 3).[22] Characterization of these new complexes was straightforward following their analytical and spectroscopic data (details are given in the Experimental Section). In particular, the $^{31}P\{^1H\}$ NMR spectra were very informative, showing a strong downfield shift of the $Ph_nP$ signal ($\delta_P$ = 25.9 (**7**), 13.8 (**8**) and 1.7 (**9**) ppm) with respect to that shown by the corresponding free phosphines ($\delta_P$ = -23.9 (**4**), -42.3 (**5**) and -57.4 (**6**) ppm), as a consequence of the direct coordination of this group to ruthenium. $^1H$ and $^{13}C\{^1H\}$ NMR spectra also showed the expected signals for the $\eta^6$-coordinated *p*-cymene unit and the corresponding *P*-donor ligand. For the latter, characteristic low-field resonances were observed for the olefinic =CH unit of the thiazolyl rings at $\delta_H$ = 7.28-7.56 (d, $J_{PH}$ = 4.8-5.4 Hz) ppm and $\delta_C$ = 135.1-137.2 (d, $J_{PC}$ = 8.8-10.9 Hz, or br signal) ppm. Concerning the solubility in water of these ruthenium complexes, as observed for the free ligands, it was dependent on the number of thiazolium units present in their structures (< 1 g/L (**7**), 7 g/L (**8**) and 8 g/L (**9**)).[23]




**Scheme 3** Synthesis of the water-soluble arene-ruthenium(II) complexes **7-9**.

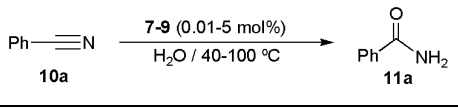




The ability of complexes **7-9** to promote the catalytic hydration of nitriles to primary amides in water was evaluated employing benzonitrile (**10a**) as model substrate (results are collected in Table 1). As the initial reaction conditions we took those previously employed with complexes **A-F** (Fig. 1), *i.e.* the use of a 0.33 M solution of the substrate in water, a ruthenium loading of 5 mol% and a working temperature of 100 ºC.[15a,b,d,f,h] Under these conditions, all the complexes synthesized were found to be active catalysts, providing benzamide (**11a**) as the unique reaction product in ≥ 95% GC-yield after 0.75-7 h of heating (entries 1-3). As previously observed with **A-F**, in no case traces of benzoic acid were detected by GC in the crude reaction mixtures. Remarkably, a direct relationship between the number of thiazolium units present in the phosphine ligands and the catalytic activity was observed, the best results being obtained with complex **9**, *i.e.* that containing the largest number of these units, which was able to generate benzamide quantitatively in only 0.75 h (entry 3). The differences in reactivity found can not be attributed to the different solubilities of the catalysts in water since, under the reaction conditions employed, all of them completely dissolved in the medium. The increase of activity with the number of thiazolium units may be therefore related to the growing number of hydrogen acceptor groups (sulphur atoms and pendant $NH_2$ units) able to activate the nucleophilic water molecules. The turnover frequency (TOF) value reached with complex **9** under these standard reaction conditions was 27 $h^{-1}$, a number that compares favourably with those described for the same reaction catalyzed by complexes **A-F** (TOF = 3-20 $h^{-1}$).[15a,b,d,f,h]

**Table 1** Catalytic hydration of benzonitrile (**10a**) to benzamide (**11a**) in water using the arene-ruthenium(II) complexes **7-9**.[a]




**10a** **11a**

| Entry | Catalyst | Temp. | Time | Yield of **11a**[b] |
|---|---|---|---|---|
| 1 | **7** (5 mol%) | 100 ºC | 7 h (0.5 h) | 95% (31%) |
| 2 | **8** (5 mol%) | 100 ºC | 3 h (0.5 h) | > 99% (53%) |
| 3 | **9** (5 mol%) | 100 ºC | 0.75 h (0.5 h) | > 99% (94%) |
| 4 | **9** (3 mol%) | 100 ºC | 1.5 h | > 99% |
| 5 | **9** (2 mol%) | 100 ºC | 3 h | > 99% |
| 6 | **9** (0.01 mol%) | 100 ºC | 168 h | 98% |
| 7 | **9** (5 mol%) | 80 ºC | 3 h | > 99% |
| 8 | **9** (5 mol%) | 60 ºC | 24 h | > 99% |
| 9 | **9** (5 mol%) | 40 ºC | 48 h | 95% |

[a] Reactions performed under $N_2$ atmosphere starting from 1 mmol of benzonitrile (0.33 M in water). [b] Yields determined by GC (uncorrected GC areas).

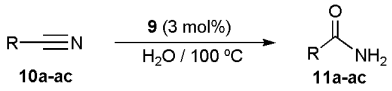
As shown in entries 4 and 5, lower metal loadings (2-3 mol% of Ru) were tolerated without a drastic increase in the reaction times. The productivity of **9** was further explored using a metal loading of only 0.01 mol% (entry 6). To our delight, almost complete (98%) formation of benzamide was achieved after 7 days of heating (TON = 9800), making **9** an highly active and long-lived nitrile hydration catalyst. Also worthy of note is the wide range of temperatures in which this complex is able to operate (entries 7-9). For example, at 40 ºC, 95% conversion of benzonitrile into benzamide was reached within 48 h using a metal loading of 5 mol% (entry 9). In our knowledge, the catalyst systems able to operate at such a low temperature are restricted to $[\{Rh(\mu\text{-OMe})(cod)\}_2]/PCy_3$[11] and [RhBr(PIN)(cod)],[12] both active in organic media, and the heterogeneous one $CeO_2$ active in water.[8d] However, in marked contrast to complex **9**, the latter is only effective for the hydration of nitriles that contain an heteroatom (N or O) adjacent to the $\alpha$ carbon of the C≡N group, being completely inoperative with other unfunctionalized nitriles such as benzonitrile.[24]

The scope of this aqueous transformation was next explored using the most active catalyst **9**. First, we focused on the hydration a wide array of functionalized benzonitriles **10b-o**, performing the catalytic reactions at 100 ºC with a ruthenium loading of 3 mol % (entries 2-15 in Table 2). As observed for benzonitrile (**10a**; entry 1), the corresponding benzamides **11b-o** were selectively generated in almost quantitative GC-yields (≥ 97%) after short reaction periods (0.5-5 h), regardless of the substitution pattern and electronic nature of the aromatic ring. Remarkably, several functional groups were tolerated, including the hydrolyzable ester one (entry 12),[25] and no over-hydrolysis to carboxylic acids was observed, thus demonstrating the great synthetic potential of complex **9**. However, we must note that, due probably to steric grounds, a remarkably longer reaction time (24 h) was needed to transform the bulkier 1-naphthylcarbonitrile (**10p**) into 1-naphthylcarboxamide (**11p**) in high yield (90% by GC; entry 16).

Catalyst **9** also hydrates efficiently heteroaromatic nitriles (**10q-s**; entries 17-19) with, for example, 3-cyanopyridine (**10q**) being quantitatively and selectively converted into industrially relevant nicotinamide (**11q**) after only 5 h of heating (entry 17).[6] The scope of **9** was further extended with success to the hydration of substrates containing alkyl-CN bonds (**10t-z**; entries 20-26) and $\alpha,\beta$-unsaturated substituents (**10aa-10ac**; entries 27-29). With the exception of the bulky cyclohexylcarbonitrile (**10y**; entry 25), which required 24 h, the reactions were completed in 1-7 h. Remarkably, hydration of chloroacetonitriles $Cl_{3-n}CH_nC{\equiv}N$ (**10u-w**) into the corresponding chloroacetamides $Cl_{3-n}CH_nC(=O)NH_2$ (**11u-w**), a particular class of compounds that exhibit biological properties and are widely used as building blocks in preparative organic chemistry,[26] proceeded cleanly using complex **9** (≥ 96% GC-yield; entries 21-23). It is also worthy of note that, neither hydration of the carbon-carbon double bond, nor side polymerization processes were observed during the hydration of acrylonitrile (**10aa**)[6] and its substituted counterparts **10ab-ac** (entries 27-29). Another important and green aspect of our current protocol is that, due to the relatively high solubility in water showed by complex **9**, isolation of the final amides required only minor amounts of organic solvents. Thus, after completion of the reaction, crystallization of the product takes place by cooling the mixture at 0 ºC in an ice bath for 4 h, thus allowing an easy separation from the aqueous solution containing **9** (details are given in the Experimental Section). Subsequent recrystallization from hot water, followed by a washing of the white crystals with hexanes led in most cases to the amides in

analytically pure form (78-93% yield).

**Table 2** Catalytic hydration of nitriles to amides in water using the arene-ruthenium(II) complex **9**.[a]




| Entry | Nitrile **10** | Time | Yield of **11**[b] |
|---|---|---|---|
| 1 | R = $C_6H_5$ (**10a**) | 1.5 h | **11a**; > 99% (91%) |
| 2 | R = 3-$C_6H_4F$ (**10b**) | 2 h | **11b**; > 99% (92%) |
| 3 | R = 4-$C_6H_4F$ (**10c**) | 2 h | **11c**; > 99% (90%) |
| 4 | R = 2-$C_6H_4Cl$ (**10d**) | 3 h | **11d**; 97% (88%) |
| 5 | R = 4-$C_6H_4Cl$ (**10e**) | 3 h | **11e**; > 99% (93%) |
| 6 | R = 4-$C_6H_4Br$ (**10f**) | 2 h | **11f**; > 99% (90%) |
| 7 | R = $C_6F_5$ (**10g**) | 0.5 h | **11g**; 99% (91%) |
| 8 | R = 3-$C_6H_4NO_2$ (**10h**) | 0.5 h | **11h**; > 99% (90%) |
| 9 | R = 2-Me-4-$C_6H_3NO_2$ (**10i**) | 1 h | **11i**; 98% (86%) |
| 10 | R = 4-$C_6H_4COH$ (**10j**) | 0.5 h | **11j**; 98% (89%) |
| 11 | R = 4-$C_6H_4COMe$ (**10k**) | 0.5 h | **11k**; 99% (87%) |
| 12 | R = 4-$C_6H_4CO_2Et$ (**10l**) | 1 h | **11l**; >99% (92%) |
| 13 | R = 3-$C_6H_4OMe$ (**10m**) | 3 h | **11m**; >99% (91%) |
| 14 | R = 4-$C_6H_4OMe$ (**10n**) | 5 h | **11n**; 98% (87%) |
| 15 | R = 4-$C_6H_4SMe$ (**10o**) | 3 h | **11o**; > 99% (93%) |
| 16 | R = 1-Naphthyl (**10p**) | 24 h | **11p**; 90% (78%) |
| 17 | R = 3-Pyridyl (**10q**) | 5 h | **11q**; > 99% (91%) |
| 18 | R = 5-Me-2-Furyl (**10r**) | 2 h | **11r**; > 99% (93%) |
| 19 | R = 2-Thienyl (**10s**) | 1 h | **11s**; > 99% (92%) |
| 20 | R = $CH_3$ (**10t**) | 1 h | **11t**; > 99% (90%) |
| 21 | R = $CH_2Cl$ (**10u**) | 1 h | **11u**; 96% (88%) |
| 22 | R = $CHCl_2$ (**10v**) | 1 h | **11v**; 97% (85%) |
| 23 | R = $CCl_3$ (**10w**) | 1 h | **11w**; 97% (86%) |
| 24 | R = *n*-$C_5H_{11}$ (**10x**) | 7 h | **11x**; 99% (89%) |
| 25 | R = *c*-$C_6H_{11}$ (**10y**) | 24 h | **11y**; 91% (80%) |
| 26 | R = $(CH_2)_3Ph$ (**10z**) | 7 h | **11z**; 99% (91%) |
| 27 | R = CH=$CH_2$ (**10aa**) | 7 h | **11aa**; >99% (91%) |
| 28 | R = (*E*)-CH=CHPh (**10ab**) | 5 h | **11ab**; 99% (86%) |
| 29 | R = (*E*)-CH=CH-4-$C_6H_4Cl$ (**10ac**) | 7 h | **11ac**; 99% (90%) |

[a] Reactions performed under $N_2$ atmosphere starting from 1 mmol of the corresponding nitrile (0.33 M in water). [b] Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate work-up are given in brackets.

For practical applications, the lifetime of a catalyst and its level of reusability are very important factors.[27] In this sense, the recycling of complex **9** was investigated using the hydration of pentafluorobenzonitrile (**10g**) as model reaction. Thus, after cooling the final reaction mixture and separation of the crystalline pentafluorobenzamide (**11g**) formed, the aqueous solution containing **9** was recovered and exposed to fresh substrate under the same experimental conditions. As shown in Fig. 2, almost quantitative conversions were reached during five consecutive cycles. The decrease in activity observed after each cycle was due to incomplete catalyst recovery during transfer of the aqueous supernatant, a fact that was evident to the naked eye by the yellowish color of the product.

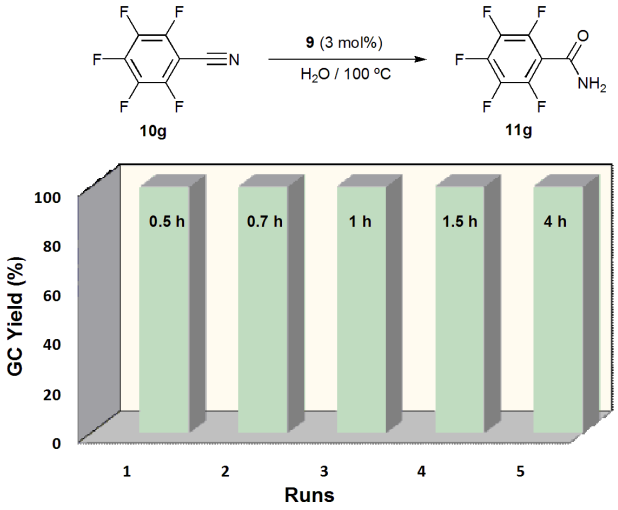
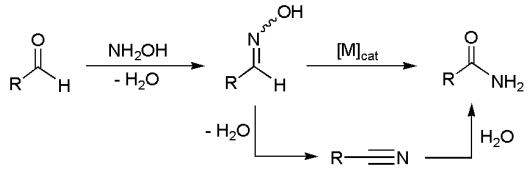



**Fig. 2** Reuse of the aqueous solution containing complex **9** in the hydration reaction of pentafluorobenzonitrile (**10g**).

In addition to the classical nitrile hydration reactions, more innovative approaches to primary amides have seen the light in recent years with the help of transition-metal catalysts.[28] In particular, the metal-catalyzed rearrangement of aldoximes is a completely atom efficient process for forming primary amides, which involves a simple dehydration/hydration sequence *via* the formation of a discrete nitrile intermediate (Scheme 4).[28,29] The ease of access to aldoximes by condensation of aldehydes with hydroxylamine derivatives has also enabled the development of catalytic routes for the direct conversion of aldehydes to primary amides (Scheme 4).[28]



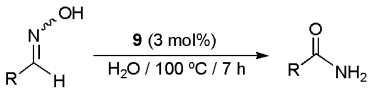

**Scheme 4** Catalytic routes to primary amides starting from aldoximes and aldehydes.

Several catalysts are presently available for both transformations in organic media but, to date, little attention has been paid to the discovery of catalytic systems able to operate in environmentally friendly aqueous media.[14] Indeed, to the best of our knowledge, complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (**C** in Fig. 1) is the only ruthenium catalyst capable of promoting these amide bond-forming reactions in water.[30] This fact, along with the excellent effectiveness shown by the arene-ruthenium(II) complex **9** in the nitrile hydration processes, encouraged us to study the utility of this complex for the catalytic rearrangement of aldoximes and the one-pot synthesis of primary amides from aldehydes in water.

As shown in Table 3, we were pleased to find that, under the same reaction conditions previously employed in the nitrile

hydration studies (0.33 M solution of the substrate in pure water, a metal loading of 3 mol% and a temperature regime of 100 ºC), the rearrangement of selected aromatic (entries 1-4), heteroaromatic (entry 5), aliphatic (entries 6-7) and *α,β*-unsaturated (entry 8) aldoximes **12a-ag** proceeded efficiently to afford the desired primary amides in ≥ 90% GC-yield after 7 h of heating.[31,32] As in the precedent case, crystallization of the product took place by cooling the reaction mixture at 0 ºC in an ice bath, thus allowing its easy purification (79-88% isolated yields) and the recycling of the aqueous solution containing **9** (four times using benzaldoxime **12a** as model substrate; up to 72% GC-yield in the fourth cycle after 7 h of reaction). It is also important to note that, compared to [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**C** in Fig. 1), complex **9** resulted more active since a higher metal loading (5 mol% of Ru) was needed with the former to attain similar conversions.[30a]

**Table 3** Catalytic rearrangement of aldoximes to amides in water using the arene-ruthenium(II) complex **9**.[a]




**12a-ag** **11a-ag**

| Entry | Aldoxime **12** | Yield of **11**[b] |
|---|---|---|
| 1 | R = $C_6H_5$ (**12a**) | **11a**; 93% (80%) |
| 2 | R = 3-$C_6H_4Cl$ (**12ad**) | **11ad**; 97% (85%) |
| 3 | R = $C_6F_5$ (**12g**) | **11g**; 96% (87%) |
| 4 | R = 4-$C_6H_4Me$ (**12ae**) | **11ae**; 91% (82%) |
| 5 | R = 3-Furyl (**12af**) | **11af**; 97% (89%) |
| 6 | R = *n*-$C_5H_{11}$ (**12x**) | **11x**; 90% (79%) |
| 7 | R = $(CH_2)_2Ph$ (**12ag**) | **11ag**; 93% (85%) |
| 8 | R = (*E*)-CH=CHPh (**12ab**) | **11ab**; 97% (88%) |

[a] Reactions performed under $N_2$ atmosphere starting from 1 mmol of the corresponding aldoxime (0.33 M in water). [b] Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate work-up are given in brackets.

To our delight complex **9** proved also active in the *one-pot* synthesis of the same primary amides **11a-ag** from the corresponding aldehydes **13a-ag**, by using hydroxylamine hydrochloride as the "$NH_2$ source" and $NaHCO_3$ as the base (Table 4). Introduction of the latter in the medium was needed to catch the HCl released during the formation of the key aldoxime intermediates **12a-ag**. Otherwise, competitive acid-catalyzed over-hydrolysis of the amides to the carboxylic acids takes place. Compared to the reactions carried out starting from the isolated aldoximes **12a-ag** slightly lower yields were in all the cases attained. However, we would like to stress that these results compete again favourably with those reported using complex [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] (**C** in Fig. 1).[30b]

**Table 4** Catalytic *one-pot* synthesis of primary amides from aldehydes and hydroxylamine hydrochloride in water using the arene-ruthenium(II) complex **9**.[a]

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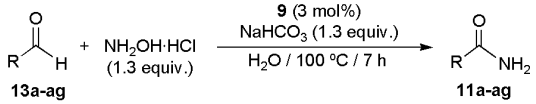
DOI: 10.1039/C3GC41201F




**13a-ag** **11a-ag**

| Entry | Aldedyde **13** | Yield of **11**[b] |
|---|---|---|
| 1 | R = $C_6H_5$ (**13a**) | **11a**; 89% (77%) |
| 2 | R = 3-$C_6H_4Cl$ (**13ad**) | **11ad**; 93% (80%) |
| 3 | R = $C_6F_5$ (**13g**) | **11g**; 92% (82%) |
| 4 | R = 4-$C_6H_4Me$ (**13ae**) | **11ae**; 87% (74%) |
| 5 | R = 3-Furyl (**13af**) | **11af**; 95% (84%) |
| 6 | R = *n*-$C_5H_{11}$ (**13x**) | **11x**; 80% (68%) |
| 7 | R = $(CH_2)_2Ph$ (**13ag**) | **11ag**; 88% (79%) |
| 8 | R = (*E*)-CH=CHPh (**13ab**) | **11ab**; 91% (80%) |

[a] Reactions performed under $N_2$ atmosphere starting from 1 mmol of the corresponding aldehyde (0.33 M in water), 1.3 mmol of $NH_2OH·HCl$ and 1.3 mmol of $NaHCO_3$. [b] Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate work-up are given in brackets.

## Conclusions

In conclusion, a new class of water-soluble phosphine ligands, consisting of *N*-protonated thiazolyl-phosphine salts, has been developed.[33] Among the group of phosphine synthesized, the structurally characterized tris(5-(2-aminothiazolyl))phosphine trihydrochloride salt **6** turned out to be an excellent auxiliary ligand in the ruthenium-catalyzed selective hydration of organonitriles to primary amides, and related amide bond forming reactions, in environmentally friendly aqueous medium, allowing fast conversions, a facile product separation and catalyst recycling. Remarkably, in all the catalytic transformations studied, activities superior to those described previously with related ruthenium complexes containing classical cage-like water-soluble phosphines or $P(NMe_2)_3$ have been obtained. The results presented herein, along with those previously reported on copper-catalyzed *N*-arylation reactions[17] and Suzuki-type cross-coupling processes,[18] clearly demonstrate the enormous potential of heteroaromatic thiazolyl-phosphines for the development of new efficient and cleaner catalytic systems.

## Experimental Section

**General methods:** Synthetic procedures were performed under inert atmosphere using vacuum-line and standard Schlenk techniques. Solvents were dried by standard methods and distilled under nitrogen before use. The thiazolyl phosphines **1-3**[17,19] and the ruthenium(II) dimer [$\{RuCl(\mu$-Cl)$(\eta^6$-*p*-cymene)$\}_2$][21] were prepared by following the methods reported in the literature. The rest of reagents employed in this work were obtained from commercial suppliers and used as received. NMR spectra were recorded with Bruker AC-200, AC-250, DPX-300 or AV-300 spectrometers. References for NMR chemical shifts are 85% $H_3PO_4$ for $^{31}P$ NMR, and $SiMe_4$ for $^1H$ and $^{13}C$ NMR. The attribution of $^{13}C$ NMR signals of **4-9** has been done using Jmod, two dimensional HBMC and HMQC, broad band, or CW $^{31}P$

decoupling experiments when necessary. The first-order peak patterns are indicated as s (singulet), d (doublet), t (triplet), q (quadruplet), sep (septuplet). Complex non-first-order signals are indicated as m (multiplet). Melting points were determined using Electrothermal digital melting point apparatus and are uncorrected. Elemental analysis and ESI-MS measurements were provided by the Analytical Services of Paul Sabatier University. GC measurements were performed on a Hewlett-Packard HP6890 equipment using a Supelco Beta-Dex™ 120 column (30 m length; 250 µm diameter).

**Preparation of diphenyl(5-(2-aminothiazolyl))phosphine hydrochloride (4):** To a stirred solution of diphenyl(5-(2-aminothiazolyl))phosphine (**1**) (1.08 g, 3.80 mmol) in methanol (15 $cm^3$) was added a 37% aqueous solution of hydrochloric acid (1.2 $cm^3$, 11.4 mmol). The reaction mixture was stirred for 30 minutes, evaporated in vacuum and freeze-dried to yield **4** as a white solid quantitatively. M.p. = 174-175 °C; $^{31}P\{^1H\}$ NMR ($CD_3OD$): $\delta$ = -23.9 (s) ppm; $^1H$ NMR ($CD_3OD$): $\delta$ = 7.51 (d, $J_{PH}$ = 4.8 Hz, 1H, 4-thiazolyl), 7.48-7.37 (m, 10H, *o*-, *m*- and *p*-phenyl) ppm; $^{13}C\{^1H\}$ NMR ($CD_3OD$): $\delta$ = 173.4 (s, 2-thiazolyl), 135.1 (d, $J_{CP}$ = 6.9 Hz, *i*-phenyl), 133.7 (d, $J_{CP}$ = 44.4 Hz, 4-thiazolyl), 132.5 (d, $J_{CP}$ = 19.9 Hz, *o*-phenyl), 129.6 (s, *p*-phenyl), 128.8 (d, $J_{CP}$ = 7.1 Hz, *m*-phenyl), 120.6 (d, $J_{CP}$ = 41.8 Hz, 5-thiazolyl) ppm; ESI-MS (methanol): *m/z* = 285.0 ($[C_{15}H_{13}N_2PS\times H]^+$, calcd. 285.0); Anal. calcd. for $C_{15}H_{14}ClN_2PS$ (320.78 g/mol): C 56.16, H 4.40, N 8.73; found: C 55.80, H 4.12, N 8.90.

**Preparation of phenylbis(5-(2-aminothiazolyl))phosphine dihydrochloride (5):** To a stirred suspension of phenylbis(5-(2-aminothiazolyl))phosphine (**2**) (2.00 g, 6.53 mmol) in methanol (20 $cm^3$) was added a 37% aqueous solution of hydrochloric acid (6.43 $cm^3$, 65.3 mmol). The reaction mixture was stirred for 30 minutes, evaporated in vacuum and freeze-dried to yield **5** as a white solid quantitatively. M.p. = 177-178 °C; $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta$ = -42.3 (s) ppm; $^1H$ NMR ($D_2O$): $\delta$ = 7.59 (d, $J_{PH}$ = 5.1 Hz, 2H, 4-thiazolyl), 7.47-7.35 (m, 5H, *o*-, *m*- and *p*-phenyl) ppm; $^{13}C\{^1H\}$ NMR ($D_2O$): $\delta$ = 173.1 (s, 2-thiazolyl), 135.3 (d, $J_{CP}$ = 44.5 Hz, 4-thiazolyl), 132.9 (s, *i*-phenyl), 131.5 (d, $J_{CP}$ = 18.7 Hz, *o*-phenyl), 130.3 (s, *p*-phenyl), 129.2 (d, $J_{CP}$ = 6.8 Hz, *m*-phenyl), 117.2 (d, $J_{CP}$ = 33.4 Hz, 5-thiazolyl) ppm; ESI-MS (methanol): *m/z* = 307.1 ($[C_{12}H_{11}N_4PS_2\times H]^+$, calcd. 307.0); Anal. calcd. for $C_{12}H_{13}Cl_2N_4PS_2$ (379.27 g/mol): C 38.00, H 3.45, N 14.77; found: C 37.69, H 3.23, N 14.38.

**Synthesis of tris(5-(2-aminothiazolyl))phosphine trihydrochloride (6):** To a stirred suspension of tris(5-(2-aminothiazolyl))phosphine (**3**) (2.07 g, 6.30 mmol) in water (15 $cm^3$) was added a 37% aqueous solution of hydrochloric acid (6.21 $cm^3$, 63.0 mmol). The reaction mixture was stirred for 30 minutes, evaporated in vacuum and freeze-dried to yield **6** as a white solid quantitatively. M.p. = 179-180 °C; $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta$ = -57.4 (s) ppm; $^1H$ NMR ($D_2O$): $\delta$ = 7.45 (d, $J_{PH}$ = 4.5 Hz, 3H, 4-thiazolyl) ppm; $^{13}C\{^1H\}$ NMR ($D_2O$): $\delta$ = 173.0 (s, 2-thiazolyl), 135.0 (d, $J_{CP}$ = 41.0 Hz, 4-thiazolyl), 114.8 (d, $J_{CP}$ = 26.9 Hz, 5-thiazolyl) ppm; ESI-MS (methanol): *m/z* = 329.0 ($[C_9H_9N_6PS_3\times H]^+$, calcd. 329.0); Anal. calcd. for $C_9H_{12}Cl_3N_6PS_3$ (437.76 g/mol): C 24.69, H 2.76, N 19.20; found: C 24.34, H 2.48, N 18.87.

**Preparation of the arene-ruthenium(II) complex 7:** A solution of $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$ (0.278 g, 0.454 mmol) and **4** (0.291 g, 0.908 mmol) in methanol (20 $cm^3$) was stirred at room temperature for 3 h. Concentration to *ca.* 5 $cm^3$, followed by the addition of pentane (*ca.* 20 $cm^3$), precipitated a red microcrystalline solid, which was filtered, washed with pentane (5 $cm^3$), and dried in vacuo. Yield: 0.483 g (85%); $^{31}P\{^1H\}$ NMR ($CD_3OD$): $\delta$ = 25.9 (s) ppm; $^1H$ NMR ($CD_3OD$): $\delta$ = 7.95-7.85 (m, 4H, *o*-phenyl), 7.70-7.57 (m, 6H, *m*- and *p*-phenyl), 7.23 (d, $J_{PH}$ = 4.8 Hz, 1H, 4-thiazolyl), 5.53 (d, $J_{HH}$ = 6.3 Hz, 2H, CH of cymene), 5.47 (d, $J_{HH}$ = 6.3 Hz, 2H, CH of cymene), 2.52 (sep, $J_{HH}$ = 6.9 Hz, 1H, C*H*$Me_2$), 1.86 (s, 3H, Me), 1.01 (d, $J_{HH}$ = 6.9 Hz, 6H, CH*Me*$_2$) ppm; $^{13}C\{^1H\}$ NMR ($CD_3OD$): $\delta$ = 172.7 (d, $J_{CP}$ = 2.5 Hz, 2-thiazolyl), 135.1 (d, $J_{CP}$ = 8.8 Hz, 4-thiazolyl), 133.5 (d, $J_{CP}$ = 10.6 Hz, *o*-phenyl), 131.8 (d, $J_{CP}$ = 48.0 Hz, *i*-phenyl), 131.7 (d, $J_{CP}$ = 2.4 Hz, *p*-phenyl), 128.7 (d, $J_{CP}$ = 10.3 Hz, *m*-phenyl), 116.0 (d, $J_{CP}$ = 45.4 Hz, 5-thiazolyl), 110.2 (d, $J_{CP}$ = 2.2 Hz, C of cymene), 97.4 (s, C of cymene), 89.5 (d, $J_{CP}$ = 4.2 Hz, CH of cymene), 87.1 (d, $J_{CP}$ = 5.7 Hz, CH of cymene), 30.2 (s, *C*H$Me_2$), 20.5 (s, CH*Me*$_2$), 16.3 (s, Me) ppm; ESI-MS (methanol): *m/z* = 555.3 ($[M - Cl - HCl]^+$, calcd. for $[C_{25}H_{27}ClN_2PRuS]^+$: 555.0); Anal. calcd. for $C_{25}H_{28}Cl_3N_2PRuS$ (626.97 g/mol): C 47.89, H 4.50, N 4.47; found: C 47.41, H 4.21, N 4.39.

**Preparation of the arene-ruthenium(II) complex 8:** A solution of $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$ (0.278 g, 0.454 mmol) and **5** (0.344 g, 0.908 mmol) in methanol (20 $cm^3$) was stirred at room temperature for 3 h. Concentration to *ca.* 5 $cm^3$, followed by the addition of pentane (*ca.* 20 $cm^3$), precipitated a red microcrystalline solid, which was filtered, washed with pentane (5 $cm^3$), and dried in vacuo. Yield: 0.510 g (82%); $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta$ = 13.8 (s) ppm; $^1H$ NMR ($D_2O$): $\delta$ = 7.86-7.75 (m, 2H, *o*-phenyl), 7.70-7.55 (m, 3H, *m*- and *p*-phenyl), 7.28 (d, $J_{PH}$ = 5.1 Hz, 2H, 4-thiazolyl), 5.66 (d, $J_{HH}$ = 6.3 Hz, 2H, CH of cymene), 5.52 (d, $J_{HH}$ = 6.3 Hz, 2H, CH of cymene), 2.28 (sep, $J_{HH}$ = 6.9 Hz, 1H, C*H*$Me_2$), 1.70 (s, 3H, Me), 1.00 (d, $J_{HH}$ = 6.9 Hz, 6H, CH*Me*$_2$) ppm; $^{13}C\{^1H\}$ NMR ($D_2O$): $\delta$ = 173.1 (d, $J_{CP}$ = 4.1 Hz, 2-thiazolyl), 137.2 (d, $J_{CP}$ = 10.9 Hz, 4-thiazolyl), 133.0 (s, *i*-phenyl), 131.9 (d, $J_{CP}$ = 11.4 Hz, *o*-phenyl), 129.7 (d, $J_{CP}$ = 11.1 Hz, *m*-phenyl), 129.1 (s, *p*-phenyl), 113.9 (d, $J_{CP}$ = 50.7 Hz, 5-thiazolyl), 110.2 (d, $J_{CP}$ = 3.5 Hz, C of cymene), 101.4 (s, C of cymene), 88.3 (d, $J_{CP}$ = 4.8 Hz, CH of cymene), 87.8 (d, $J_{CP}$ = 3.8 Hz, CH of cymene), 30.3 (s, *C*H$Me_2$), 21.0 (s, CH*Me*$_2$), 17.0 (s, Me) ppm; ESI-MS (methanol): *m/z* = 577.1 ($[M - Cl - 2HCl]^+$, calcd. for $[C_{22}H_{25}ClN_4PRuS_2]^+$: 577.0); Anal. calcd. for $C_{22}H_{27}Cl_4N_4PRuS_2$ (685.46 g/mol): C 38.55, H 3.97, N 8.17; found: C 38.01, H 3.88, N 7.87.

**Preparation of the arene-ruthenium(II) complex 9:** A solution of $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$ (0.278 g, 0.454 mmol) and **6** (0.397 g, 0.908 mmol) in water (20 $cm^3$) was stirred at room temperature for 3 h. Concentration to *ca.* 10 $cm^3$, followed by the addition of pentane (*ca.* 20 $cm^3$), precipitated a red microcrystalline solid, which was filtered, washed with pentane (5 $cm^3$), and dried in vacuo. Yield: 0.527 g (78%); $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta$ = 1.7 (s) ppm; $^1H$ NMR ($D_2O$): $\delta$ = 7.56 (d, $J_{PH}$ = 5.4 Hz, 3H, 4-thiazolyl), 5.87 (d, $J_{HH}$ = 6.0 Hz, 2H, CH of cymene), 5.58 (d, $J_{HH}$ = 6.0 Hz, 2H, CH of cymene), 2.65 (sep, $J_{HH}$ = 6.9

Hz, 1H, C*H*Me$_2$), 1.87 (s, 3H, Me), 1.18 (d, $J_{HH}$ = 6.9 Hz, 6H, CH*Me*$_2$) ppm; $^{13}C\{^1H\}$ NMR ($D_2O$): $\delta$ = 173.4 (d, $J_{CP}$ = 4.9 Hz, 2-thiazolyl), 137.8 (broad s, 4-thiazolyl), 114.0 (d, $J_{CP}$ = 5.3 Hz, C of cymene), 112.4 (d, $J_{CP}$ = 56.5 Hz, 5-thiazolyl), 102.0 (s, C of cymene), 89.6 (d, $J_{CP}$ = 4.9 Hz, CH of cymene), 87.0 (d, $J_{CP}$ = 2.9 Hz, CH of cymene), 30.8 (s, *C*HMe$_2$), 21.2 (s, CH*Me*$_2$), 17.1 (s, Me) ppm; ESI-MS (methanol): *m/z* = 635.2 ([M - 3HCl]$^+$, calcd. for [$C_{19}H_{23}Cl_2N_6PRuS_3$×H]$^+$: 634.9); Anal. calcd. for $C_{19}H_{26}Cl_5N_6PRuS_3$ (743.96 g/mol): C 30.67, H 3.52, N 11.30; found: C 29.93, H 3.38, N 10.46.

**General procedure for the catalytic hydration of nitriles:** Under nitrogen atmosphere, the corresponding nitrile (1 mmol), water (3 cm$^3$) and the ruthenium(II) catalyst **9** (0.022 g, 0.03 mmol; 3 mol%) were introduced into a teflon-capped sealed-tube and the reaction mixture stirred at 100 °C for the indicated time (see Table 2). The course of the reaction was monitored by taking regularly samples of *ca.* 20 $\mu$L which after extraction with $CH_2Cl_2$ (3 cm$^3$) were analyzed by GC. Once the reaction finished, the hot mixture was passed through a filter paper, allowed to reach the room temperature, and then kept in an ice bath for 4 h. This led to the crystallization of the corresponding primary amide, which was separated, recrystallized from hot water, washed with hexanes (2 x 5 mL) and vacuum-dried (in some cases an additional recrystallization from hot water or purification by column chromatography over silica gel, using methanol/$CH_2Cl_2$ mixtures as eluent, was needed). The identity of the amides was assessed by comparison of their $^1H$ and $^{13}C\{^1H\}$ NMR spectroscopic data with those reported in the literature and by their fragmentation in GC/MSD.

**General procedure for the catalytic rearrangement of aldoximes:** Under nitrogen atmosphere, the corresponding aldoxime (1 mmol), water (3 cm$^3$) and the ruthenium(II) catalyst **9** (0.022 g, 0.03 mmol; 3 mol%) were introduced into a teflon-capped sealed-tube and the reaction mixture stirred at 100 °C for 7 h. Following the same work-up described above, the resulting primary amides could be isolated in pure form (yields are given in Table 3).

**General procedure for the catalytic *one-pot* synthesis of primary amides from aldehydes and hydroxylamine hydrochloride:** Under nitrogen atmosphere, the corresponding aldehyde (1 mmol), hydroxylamine hydrochloride (0.090 g, 1.3 mmol), $NaHCO_3$ (0.109 g, 1.3 mmol), water (3 cm$^3$) and the ruthenium(II) catalyst **9** (0.022 g, 0.03 mmol; 3 mol%) were introduced into a teflon-capped sealed-tube and the reaction mixture stirred at 100 °C for 7 h. After this time, the mixture was evaporated to dryness, the solid residue extracted with $CH_2Cl_2$ (20 cm$^3$) and filtered over kieselguhr. Evaporation of the extract led to a solid, which was recrystallized from hot water, washed with hexanes (2 x 5 cm$^3$) and vacuum-dried (yields are given in Table 4).

## Acknowledgements

This work was supported by the Spanish MINECO (projects CTQ2010-14796/BQU and CSD2007-00006). Thanks are due to Dr G.V.Oshovsky who prepared crystals of compound **6** suitable for X -Ray diffraction studies.

## Notes and references

[a] *Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Departamento de Química Orgánica e Inorgánica, IUQOEM, Universidad de Oviedo, Julián Clavería 8, 33006 Oviedo, Spain. Phone: (+34)985-103-453. Fax: (+34)985-103-446. E-mail: vcm@uniovi.es*

[b] *Laboratoire de Chimie de Coordination UPR 8241 CNRS, 205 route de Narbonne, 31077 Toulouse Cedex 04, France. Phone: (+33)561-333-123. Fax: (+33)561-553-003. E-mail: jean-pierre.majoral@lcc-toulouse.fr*

[c] *Centre of Molecular and Macromolecular Studies, The Polish Academy of Sciences, Sienkiewicza 112, 90363 Lodz, Poland. Fax: (+48)-426-847-126. E-mail: zabloc@cbmm.lodz.pl*

† Electronic Supplementary Information (ESI) available: A CIF file containing crystallographic data, an ORTEP plot of the structure of **6**, with selected bonding parameters, and copies of the $^1H$ and $^{13}C\{^1H\}$ NMR spectra of selected amides synthesized in this work. See DOI: 10.1039/b000000x/

‡ CCDC 945999 contains the supplementary crystallographic data for compound **6**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif and are contained in the ESI file.

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23 Surprisingly, despite the presence of protonable $NH_2$ groups, the solubility of complexes **7-9** at pH 5 (potassium phosphate buffer) was lower than that observed in pure water (up to 0.2 g/L for **9**).

24 (*a*) Addition of a chloride abstractor ($AgNO_3$) to the medium did not allow to improve the catalytic activity of complex **9**. This fact suggests that rapid dissociation of the chloride ligands, allowing the effective coordination of benzonitrile to the metal, takes place in aqueous solution; (*b*) The activity of complex **9** at pH 5 (potassium phosphate buffer) was remarkably lower than in neutral water (19 h of heating at 100 ºC were needed to quantitatively convert benzonitrile into benzamide using 3 mol% of **9**).

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DOI: 10.1039/C3GC41201F

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32 Complexes **7** and **8** proved to be also active in the rearrangement of (*E*)-benzaldoxime (**12a**) to benzamide (**11a**) but, under identical reaction conditions, a longer reaction time (24 h) was needed to generate **11a** in high GC-yield (70% and 85%, respectively).
33 Examples of water-soluble heteroaryl-phosphines are rare: see ref. 20*d*.