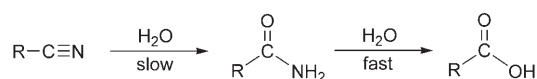


Selective Ruthenium-Catalyzed Hydration of Nitriles to Amides in Pure Aqueous Medium Under Neutral Conditions

Victorio Cadierno,* Javier Francos, and José Gimeno*[a]

Hydration of nitriles to generate the corresponding amides is an important transformation from both academic and industrial points of view. Amides not only constitute versatile building blocks in synthetic organic chemistry,^[1] but also exhibit a wide range of industrial applications^[2,3] and pharmacological interest.^[4] Nitrile hydration can be conventionally achieved in the presence of strong acid or base catalysts,^[1,5] but major drawbacks of these classical methods are: 1) the harsh conditions usually required which precludes the presence of sensitive functional groups, and 2) the reactions are difficult to stop at the amide stage and further hydrolysis to the carboxylic acid often takes place, especially in basic media (see Scheme 1). Moreover, from an



Scheme 1. Nitrile hydration and amide hydrolysis reactions.

industrial perspective, the final neutralization step, either in the acid- or base-catalyzed reactions, leads to extensive salt formation with inconvenient product contamination and pollution effects.

Extreme acidity and basicity can be avoided by using transition-metal complexes. Activation of the C≡N bond occurs through coordination to the metal atom, thus enhancing the rate of the hydration step.^[6,7] However, despite the high number of metal-mediated hydration of nitriles report-

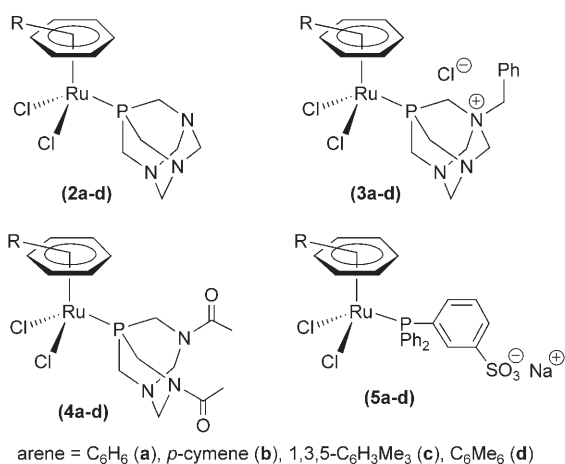
ed to date, only a few complexes can act as selective catalysts to form amides.^[6] Relevant examples, among others, are: the Murahashi's ruthenium dihydride [RuH₂(PPh₃)₄],^[8] the Parkins's platinum hydride [PtH(PMe₂OH)-(PMe₂O)₂H],^[9] the acetylacetonate complex *cis*-[Ru(acac)₂(PPh₂py)₂] (py = pyridyl)^[10] and the recently described Rh^I-based system [{Rh(μ-OMe)(cod)}₂]/PCy₃ (cod = 1,5-cyclooctadiene, Cy = cyclohexyl),^[11] all of them showing a remarkable activity. In contrast to these catalytic processes performed in organic solvents, and despite the growing interest to develop environmentally benign and safety processes, metal catalysts able to promote such a transformation in pure aqueous media are much scarcer (water is one of the best choices to replace organic solvents because of its low cost, availability, and nontoxic nature).^[12,13] Moreover, the practical application of these homogeneous catalysts, including rhodium,^[14] palladium,^[15] iridium,^[16] molybdenum,^[17] nickel,^[18] and zinc^[19] complexes,^[20] shows serious drawbacks mainly due to their low activities and very limited scope of the substrates.

All these facts prompted us to search for more efficient and versatile catalysts. Thus, following with our interest in ruthenium-catalyzed reactions in aqueous media,^[21] herein we report that the readily available^[22] and water-soluble ruthenium(II) complexes [RuCl₂(η⁶-arene)(PTA)] (**2a-d**; PTA = 1,3,5-triaza-7-phosphaadamantane), [RuCl₂(η⁶-arene)(PTA-Bn)] (**3a-d**; PTA-Bn = 1-benzyl-3,5-diaza-1-azonia-7-phosphaadamantane chloride), [RuCl₂(η⁶-arene)(DAPTA)] (**4a-d**; DAPTA = 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane) and [RuCl₂(η⁶-arene)(TPPMS)] (**5a-d**; TPPMS = *meta*-sulfonatophenyl)diphenylphosphane sodium salt) can be used as catalysts for the hydration of nitriles in pure aqueous media and under neutral conditions. Among them, the hexamethylbenzene derivative [RuCl₂(η⁶-C₆Me₆)(PTA-Bn)] (**3d**) has shown a remarkable activity and an unprecedented tolerance to functional groups.^[23]

Firstly, the hydration of benzonitrile was studied as a model reaction. Thus, in a typical experiment, the ruthenium precursor (5 mol % of Ru) was added to a 0.33 M aqueous

[a] Dr. V. Cadierno, J. Francos, Prof. Dr. J. Gimeno
Departamento de Química Orgánica e Inorgánica
Instituto Universitario de Química Organometálica "Enrique Moles"
(Unidad Asociada al CSIC), Universidad de Oviedo
Julián Clavería 8, 33006 Oviedo (Spain)
Fax: (+34) 98-510-3446
E-mail: vcm@uniovi.es
jgh@uniovi.es

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200800847>.



solution of benzonitrile at 100 °C, the course of the reaction being monitored by gas chromatography. The results are summarized in Table 1.

Table 1. Ru-catalyzed hydration of benzonitrile to benzamide in water.^[a]

$$\text{Ph-C}\equiv\text{N} \xrightarrow[\text{H}_2\text{O} / 100\text{ }^\circ\text{C}]{5\text{ mol}\% \text{ of Ru}} \text{Ph-C(=O)-NH}_2$$

| Entry | Catalyst | S [mg mL ⁻¹] ^[b] | <i>t</i> [h] | Yield [%] ^[c] | TOF [h ⁻¹] ^[d] |
|-------|-----------|---|--------------|--------------------------|---------------------------------------|
| 1 | 2a | 50.0 | 9 | 98 | 2.2 |
| 2 | 2b | 10.1 | 8 | 99 | 2.5 |
| 3 | 2c | 33.3 | 5 | 99 | 4.0 |
| 4 | 2d | 9.1 | 4 | 99 | 5.0 |
| 5 | 3a | 16.0 | 10 | 99 | 2.0 |
| 6 | 3b | 12.5 | 4 | 99 | 5.0 |
| 7 | 3c | 13.5 | 4 | 99 | 5.0 |
| 8 | 3d | 25.0 | 2 | 99 | 9.9 |
| 9 | 4a | 6.3 | 19 | 99 | 1.0 |
| 10 | 4b | 6.3 | 9 | 98 | 2.2 |
| 11 | 4c | 9.0 | 8 | 98 | 2.5 |
| 12 | 4d | 8.3 | 9 | 98 | 2.2 |
| 13 | 5a | 6.3 | 48 | 69 | <1 |
| 14 | 5b | 5.0 | 48 | 81 | <1 |
| 15 | 5c | 10.0 | 48 | 85 | <1 |
| 16 | 5d | 5.6 | 48 | 93 | <1 |

[a] Reactions performed under N₂ atmosphere at 100 °C using 1 mmol of benzonitrile (0.33 M in water). [Substrate]/[Ru] ratio = 100:5. [b] Solubility of the catalyst in water at 20 °C. [c] Yield of benzamide determined by GC. [d] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case.

All the complexes checked were found to be active and selective catalysts in the hydration process providing benzamide as the unique reaction product (benzoic acid was not detected by GC in the crude reaction mixtures). As shown in the table, no direct solubility/activity relationship was observed. Interestingly, the nature of the phosphine ligand played a crucial role on the efficiency of the process. Thus, the best results were obtained using complexes **2,3,4a-d**, all bearing a nitrogen-containing ligand (PTA, PTA-Bn or DAPTA), which led to benzamide in almost quantitative yield (≥ 98 %) after 2–19 h (entries 1–12). Among them, the

highest rate was achieved with the hexamethylbenzene derivative **3d** (turnover frequency (TOF) = 9.9 h⁻¹; entry 8). In contrast, with the sulfonated species **5a-d** longer reaction times (48 h) were required to attain good conversions (69–93 % yield; entries 13–16). This seems to indicate that nucleophilic attack of water on the metal-coordinated nitrile may be facilitated by hydrogen bonding with the nitrogen-containing ligands.^[24,25] It is worth noting that within the four series of catalysts studied, appreciable differences in activity were observed in function of the arene ligand used. The rate order observed, that is, C₆Me₆ > 1,3,5-C₆H₃Me₃ > *p*-cymene > C₆H₆, indicates clearly that higher performances are found for the more sterically demanding and electron-rich arenes.

The most active complex, that is, **3d**, was found to be an efficient catalyst for the selective hydration of a large number of other nitriles, proving the wide scope and synthetic utility of this catalytic transformation. Thus, as observed for benzonitrile, other aromatic and heteroaromatic substrates could be selectively transformed into the corresponding amides regardless of their substitution pattern and electronic nature (see Table 2). The reactions, which were all performed with a 5 mol% catalyst loading, led to the de-

Table 2. Hydration of aromatic nitriles catalyzed by **3d** in water.^[a]

$$\text{Ar-C}\equiv\text{N} \xrightarrow[\text{H}_2\text{O} / 100\text{ }^\circ\text{C}]{\mathbf{3d} (5\text{ mol}\%)} \text{Ar-C(=O)-NH}_2$$

| Entry | Substrate (Ar) | <i>t</i> [h] | Yield [%] ^[b] | TOF [h ⁻¹] ^[c] |
|-------|--|--------------|--------------------------|---------------------------------------|
| 1 | Ph | 2 | 99 (86) | 9.9 |
| 2 | 2-C ₆ H ₄ F | 2 | 99 (88) | 9.9 |
| 3 | 3-C ₆ H ₄ F | 2 | 99 (83) | 9.9 |
| 4 | 4-C ₆ H ₄ F | 2 | 98 (85) | 9.8 |
| 5 | 2-C ₆ H ₄ Cl | 3 | 97 (81) | 6.5 |
| 6 | 3-C ₆ H ₄ Cl | 1 | 98 (77) | 19.6 |
| 7 | 4-C ₆ H ₄ Cl | 1 | 98 (79) | 19.6 |
| 8 | 2-C ₆ H ₄ Br | 3 | 98 (68) | 6.5 |
| 9 | 3-C ₆ H ₄ Br | 1 | 99 (91) | 19.8 |
| 10 | 4-C ₆ H ₄ Br | 2 | 99 (89) | 9.9 |
| 11 | 3-C ₆ H ₄ NO ₂ | 3 | 99 (82) | 6.6 |
| 12 | 2-Me-4-C ₆ H ₄ NO ₂ | 4 | 99 (74) | 5.0 |
| 13 | 3-C ₆ H ₄ Me | 3 | 99 (78) | 6.6 |
| 14 | 4-C ₆ H ₄ Me | 2 | 98 (71) | 9.8 |
| 15 | 2-C ₆ H ₄ OH | 5 | 99 (84) | 4.0 |
| 16 | 3-C ₆ H ₄ OMe | 2 | 99 (80) | 9.9 |
| 17 | 4-C ₆ H ₄ OMe | 3 | 99 (83) | 6.6 |
| 18 | 4-C ₆ H ₄ SMe | 2 | 96 (76) | 9.6 |
| 19 | 3-C ₆ H ₄ NH ₂ | 1 | 96 (82) | 19.2 |
| 20 | C ₆ F ₅ | 1 | 98 (75) | 19.6 |
| 21 | 4-C ₆ F ₄ NH ₂ | 3 | 98 (79) | 6.5 |
| 22 | 4-C ₆ H ₄ C(=O)Me | 3 | 99 (80) | 6.6 |
| 23 | 4-C ₆ H ₄ C(=O)H | 3 | 99 (83) | 6.6 |
| 24 | 4-C ₆ H ₄ C(=O)OEt | 1 | 91 (69) | 18.2 |
| 25 | 4-C ₆ H ₄ C≡CSiMe ₃ | 15 | 98 (79) | 1.3 |
| 26 | piperonyl | 2 | 97 (85) | 9.7 |
| 27 | 1-naphthyl | 5 | 96 (89) | 3.8 |
| 28 | 5-Me-2-furyl | 3 | 99 (83) | 6.6 |
| 29 | 2-Tienyl | 3 | 99 (81) | 6.6 |

[a] Reactions performed under N₂ atmosphere at 100 °C using 1 mmol of the corresponding nitrile (0.33 M in water). [Substrate]/[Ru] ratio = 100:5. [b] Yield of the amide determined by GC (isolated yields are given in brackets). [c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case.

sired products in $\geq 91\%$ GC yield after 1–5 h. Subsequent purification by column chromatography on silica gel provided analytically pure samples of the amides which were isolated in 68–91% yield. Concerning the tolerance of functional groups, this methodology is compatible with the presence of halide (entries 2–10, 20 and 21), nitro (entries 11 and 12), hydroxy (entry 15), ether (entries 16, 17, and 26), thioether (entry 18), amino (entries 19 and 21), ketone (entry 22), aldehyde (entry 23), ester (entry 24), and alkyne (entry 25) substituents on the aromatic ring. Such a generality had never been demonstrated in aqueous media. Although a longer reaction time was required (15 h), it is worth noting the selective formation of 4-(trimethylsilyl-ethyl)benzamide starting from 4-(trimethylsilyl-ethyl)benzocyanide (entry 25), since 1) no hydrolytic cleavage of the C–Si bond took place and 2) the $C\equiv C$ bond remained completely unreacted despite of the known ability of ruthenium complexes to promote alkyne hydration processes.^[26]

Table 3. Hydration of alkyl-nitriles catalyzed by **3d** in water.^[a]

$$\text{Alk}-\text{C}\equiv\text{N} \xrightarrow[\text{H}_2\text{O} / 100^\circ\text{C}]{\mathbf{3d} (5 \text{ mol}\%)} \text{Alk}-\text{C}(=\text{O})\text{NH}_2$$

| Entry | Substrate (Alk) | <i>t</i> [h] | Yield [%] ^[b] | TOF [h ⁻¹] ^[c] |
|-------|---|--------------|--------------------------|---------------------------------------|
| 1 | <i>n</i> -C ₅ H ₁₁ | 5 | 98 (83) | 3.9 |
| 2 | <i>n</i> -C ₆ H ₁₃ | 8 | 95 (77) | 2.4 |
| 3 | Cy | 5 | 98 (80) | 3.9 |
| 4 | CH ₂ -4-C ₆ H ₄ Cl | 2 | 97 (84) | 9.7 |
| 5 | CH ₂ OPh | 4 | 99 (90) | 5.0 |
| 6 | CH ₂ SO ₂ Ph | 6 | 99 (87) | 3.3 |
| 7 | CH ₂ NPh(CH ₂ CH ₂ OH) | 6 | 95 (83) | 3.2 |
| 8 | CH ₂ -2-Thienyl | 3 | 99 (81) | 6.6 |
| 9 | (CH ₂) ₂ Ph | 3 | 97 (85) | 6.5 |
| 10 | (CH ₂) ₂ OPh | 2 | 99 (86) | 9.9 |
| 11 | (CH ₂) ₃ Ph | 5 | 97 (79) | 3.9 |
| 12 | CH=CH ₂ | 5 | 96 (77) | 3.8 |
| 13 | (<i>Z</i>)-CH=CH <i>Et</i> | 3 | 97 (80) | 6.5 |
| 14 | (<i>E</i>)-CH=CHPh | 2 | 95 (75) | 9.5 |
| 15 | (<i>E</i>)-CH=CH-4-C ₆ H ₄ Cl | 2 | 98 (82) | 9.8 |
| 16 | 5-norbornen-2-yl ^[d] | 3 | 96 (78) ^[d] | 6.4 |

[a] Reactions performed under N₂ atmosphere at 100°C using 1 mmol of the corresponding nitrile (0.33 M in water). [Substrate]:[Ru] ratio = 100:5. [b] Yield of the amide determined by GC (isolated yields are given in brackets). [c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case. [d] Both as a mixture of the corresponding *endo* and *exo* isomers in ca. 3:2 ratio.

As shown in Table 3, this aqueous process is not restricted to aromatic nitriles, the hydration of substrates containing alkyl–CN bonds being readily (≤ 8 h) and efficiently ($\geq 95\%$ GC yields) achieved under the standard reaction conditions. Remarkably, the industrially important hydration of acrylonitrile proceeded cleanly using **3d** to afford acrylamide in 96% GC yield after 5 h (77% isolated yield; entry 12).^[3] Neither hydration of the carbon–carbon double bond nor polymerization of acrylonitrile and/or acrylamide occurred. The same behavior was also observed for the related α,β -unsaturated nitriles *cis*-2-pentenitrile (entry 13), cinnamonitrile (entry 14), and 4-chlorocinnamonitrile

(entry 15). Sulfonyl groups are also tolerated in this transformation (entry 6).

Interestingly, although water is not an ideal solvent to perform microwave-assisted synthesis,^[27] preliminary studies have shown that the catalytic activity of complex **3d** can be

Table 4. Hydration of nitriles catalyzed by **3d** in water under MW irradiation.^[a]

$$\text{R}-\text{C}\equiv\text{N} \xrightarrow[\text{H}_2\text{O} / 150^\circ\text{C}]{\mathbf{3d} (5 \text{ mol}\%)} \text{R}-\text{C}(=\text{O})\text{NH}_2$$

MW (80W)

| Entry | Substrate (R) | <i>t</i> [min] | Yield [%] ^[b] | TOF [h ⁻¹] ^[c] |
|------------------|-------------------------------------|----------------|--------------------------|---------------------------------------|
| 1 | Ph | 15 | 96 | 76.8 |
| 2 ^[d] | Ph | 75 | 98 | 15.7 |
| 2 ^[e] | Ph | 45 | 95 | 126.7 |
| 3 | 2-C ₆ H ₄ F | 30 | 96 | 38.4 |
| 4 | 3-C ₆ H ₄ F | 30 | 98 | 39.2 |
| 5 | 4-C ₆ H ₄ F | 30 | 98 | 39.2 |
| 6 | 3-C ₆ H ₄ Cl | 15 | 95 | 76.0 |
| 7 | 3-C ₆ H ₄ Me | 30 | 98 | 39.2 |
| 8 | 4-C ₆ H ₄ Me | 45 | 99 | 26.4 |
| 9 | 3-C ₆ H ₄ OMe | 20 | 99 | 59.4 |
| 10 | (CH ₂) ₂ Ph | 40 | 96 | 28.8 |
| 11 | (CH ₂) ₂ OPh | 40 | 99 | 29.7 |

[a] Reactions performed under N₂ atmosphere using 1 mmol of the corresponding nitrile (0.33 M in water). [Substrate]:[Ru] ratio = 100:5. A CEM Discover[®] S-Class microwave was used (80W, 150°C, with cooling to optimize the power). [b] Yield of the amide determined by GC. [c] Turnover frequencies ((mol product/mol Ru)/time) were calculated at the time indicated in each case. [d] Reaction performed at 100°C. [e] Reaction performed with a [Substrate]/[Ru] ratio = 100:1.

accelerated by using microwave (MW) irradiation (see Table 4). For example, using the same substrate/Ru ratio (100:5), a TOF value of 76.8 h⁻¹ could be reached in the hydration reaction of benzonitrile (entry 1 in Table 4) versus 9.9 h⁻¹ under conventional heating (entry 1 in Table 2). More interestingly, the use of MW irradiation allows the reduction of the catalyst loading. Thus, using only 1 mol% of **3d**, benzonitrile could be transformed into benzamide in 95% GC yield after only 45 min leading to a TOF value of 126.7 h⁻¹ (entry 3 in Table 4). Such a TOF value has never been reached in aqueous media under neutral conditions.^[14–20]

In summary, a novel catalytic system for the selective hydration of organonitriles to amides in aqueous media and under neutral conditions, namely [RuCl₂(η⁶-C₆Me₆)(PTA-Bn)] (**3d**), has been discovered. The following features of complex **3d** merit special mention: 1) it represents a rare example of ruthenium species able to perform nitrile hydrations in water;^[23] 2) it has shown a remarkable activity, being the most efficient catalyst reported to date in aqueous media; and 3) it has demonstrated an unprecedented tolerance to functional groups. All these facts confer the synthetic methodology reported herein genuine potential for practical application in organic chemistry.^[28] It is also worth noting that the effect of microwaves on the catalytic nitrile hydration process has been explored for the first time, the rate enhancement observed deserving a more detailed study.

Efforts to assess the scope, limitations and synthetic applications of this aqueous transformation under MW irradiation, as well as a complete mechanistic study, are now underway in our laboratory.

Experimental Section

General procedure for the catalytic reactions: Under a nitrogen atmosphere, the ruthenium catalyst **3d** (31 mg, 5 mol% of Ru), water (3 mL) and the corresponding nitrile (1 mmol) were introduced into a sealed tube and the reaction mixture stirred at 100°C for the indicated time (see Tables 1–3). The course of the reaction was monitored by regular sampling and analysis by GC. After elimination of the solvent after reduced pressure, the crude reaction mixture was purified by column chromatography over silica gel using diethyl ether as eluent. The identity of the resulting amides was assessed by comparison of their ¹H and ¹³C{¹H} NMR spectroscopic data with those reported in the literature and by their fragmentation in GC/MS.

Acknowledgements

This work was supported by the Ministerio de Educación y Ciencia (MEC) of Spain (Project CTQ2006-08485/BQU and Consolider Ingenio 2010 (CSD2007-00006)). J.F. and V.C. thank MEC and the European Social Fund for the award of a Ph.D. grant and a “Ramón y Cajal” contract, respectively.

Keywords: amides • homogeneous catalysis • hydration • nitriles • ruthenium

- [1] a) *The Chemistry of Amides* (Ed.: J. Zabicky), Wiley-Interscience, New York, **1970**; b) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science* (Eds.: A. Greenberg, C. M. Breneman, J. F. Liebman), Wiley, New York, **2000**.
- [2] I. Johansson in *Kirk-Othmer Encyclopedia of Chemical Technology*, Vol. 2, 5th ed., Wiley, New York, **2004**, pp. 442–463.
- [3] Acrylamide is one of the most important commodity chemicals and is used in coagulants, soil conditioners, and stock additives for paper treatment and paper sizing, and for adhesives, paints, and petroleum recovering agents. Hydration of acrylonitrile, by using copper or enzymatic catalysis, produces annually more than 2×10^5 tons of acrylamide, representing the main route for the manufacture of this chemical. See, for example: H. Yamada, M. Kobayashi, *Biosci. Biotechnol. Biochem.* **1996**, *60*, 1391–1400, and references therein.
- [4] See, for example: a) S. Rivara, A. Lodola, M. Mor, A. Bedini, G. Spadoni, V. Lucini, M. Pannacci, F. Frascini, F. Scaglione, R. Ochoa Sanchez, G. Gobbi, G. Tarzia, *J. Med. Chem.* **2007**, *50*, 6618–6626; b) A. Bhattacharya, B. P. Scott, N. Nasser, H. Ao, M. P. Maher, A. E. Dubin, D. M. Swanson, M. P. Shankley, A. D. Wickenden, S. R. Chaplan, *J. Pharmacol. Exp. Ther.* **2007**, *323*, 665–674.
- [5] *Methoden Org. Chem. (Houben Weyl) 4th ed. 1952-, Vol. E5(2)*, **1985**, pp. 1024–1031.
- [6] a) An excellent and recent review on metal-mediated and metal-catalyzed nitrile hydration is available: V. Yu. Kukushkin, A. J. L. Pombeiro, *Inorg. Chim. Acta* **2005**, *358*, 1–21; b) for a general review on the reactivity of metal-activated nitriles, see: V. Yu. Kukushkin, A. J. L. Pombeiro, *Chem. Rev.* **2002**, *102*, 1771–1802.
- [7] The use of enzymes (nitrile hydratases) also represents an appealing alternative to the classical methods. For recent reviews on this topic, see: a) M. Kobayashi, S. Shimizu, *Curr. Opin. Chem. Biol.* **2000**, *4*, 95–102; b) I. Endo, M. Nojori, M. Tsujimura, M. Nakasako, S. Nagashima, M. Yohda, M. Odaka, *J. Inorg. Biochem.* **2001**, *83*, 247–253.
- [8] a) S.-I. Murahashi, S. Sasao, E. Saito, T. Naota, *J. Org. Chem.* **1992**, *57*, 2521–2523; b) S.-I. Murahashi, S. Sasao, E. Saito, T. Naota, *Tetrahedron* **1993**, *49*, 8805–8826; c) S.-I. Murahashi, H. Takaya, *Acc. Chem. Res.* **2000**, *33*, 225–233.
- [9] a) T. Ghaffar, A. W. Parkins, *Tetrahedron Lett.* **1995**, *36*, 8657–8660; b) J. Akisanya, A. W. Parkins, J. W. Steed, *Org. Process Res. Dev.* **1998**, *2*, 274–276; c) T. Ghaffar, A. W. Parkins, *J. Mol. Catal. A* **2000**, *160*, 249–261; d) X.-B. Jiang, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Org. Chem.* **2004**, *69*, 2327–2331.
- [10] T. Oshiki, H. Yamashita, K. Sawada, M. Utsunomiya, K. Takahashi, K. Takai, *Organometallics* **2005**, *24*, 6287–6290.
- [11] A. Goto, K. Endo, S. Saito, *Angew. Chem.* **2008**, *120*, 3663–3665; *Angew. Chem. Int. Ed.* **2008**, *47*, 3607–3609.
- [12] One of the challenges of today’s chemists is to move away from highly volatile, environmentally harmful, and/or biologically incompatible organic solvents; see, for example: a) J. M. DeSimone, *Science* **2002**, *297*, 799–803; b) W. M. Nelson in *Green Solvents for Chemistry, Perspectives and Practice*, Oxford University Press, New York, **2003**; c) R. A. Sheldon, *Green Chem.* **2005**, *7*, 267–278; d) D. J. Adams, P. J. Dyson, S. J. Taverner in *Chemistry in Alternative Reaction Media*, Wiley, New York, **2004**; e) C. K. Z. Andrade, L. M. Alves, *Curr. Org. Chem.* **2005**, *9*, 195–218.
- [13] For references dealing with stoichiometric and catalytic organic synthesis in aqueous media, see: a) *Aqueous-Phase Organometallic Catalysis: Concepts and Applications* (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **1998**; b) *Aqueous Organometallic Catalysis* (Eds.: I. T. Horváth, F. Joó), Kluwer, Dordrecht, **2001**; c) C.-J. Li, T. H. Chan in *Comprehensive Organic Reactions in Aqueous Media*, Wiley, New York, **2007**; d) *Organic Reactions in Water: Principles, Strategies and Applications* (Ed.: U. M. Lindström), Blackwell, Oxford, **2007**.
- [14] The catalytic system $[\{\text{Rh}(\mu\text{-Cl})(\text{cod})\}_2]/\text{TPPTS}$ (TPPTS = tris(3-sulfonatophenyl)phosphine sodium salt) has been employed in the hydration of acetonitrile to acetamide, in water at 80°C, under basic conditions (TOF values up to 207 h^{-1}): M. C. K.-B. Djoman, A. N. Ajjou, *Tetrahedron Lett.* **2000**, *41*, 4845–4849.
- [15] The complex $[\text{PdCl}(\text{OH})(\text{bipy})(\text{H}_2\text{O})]$ (bipy = 2,2'-bipyridine) was found to catalyze the selective hydration of acetonitrile and acrylonitrile to the corresponding amides, in water at 76°C, under acidic conditions (TOF values up to 29 h^{-1}): a) G. Villain, G. Constant, A. Gaset, P. Kalck, *J. Mol. Catal.* **1980**, *7*, 355–364; b) G. Villain, P. Kalck, A. Gaset, *Tetrahedron Lett.* **1980**, *21*, 2901–2904; c) G. Villain, A. Gaset, P. Kalck, *J. Mol. Catal.* **1981**, *12*, 103–111.
- [16] The iridium(I) complex $[\text{IrH}(\text{CO})(\text{TPPTS})_2]$ was able to catalyze the selective hydration of several nitriles, in water at 100°C, under neutral conditions (TOF values up to 14 h^{-1}): C. S. Chin, S. Y. Kim, K.-S. Joo, G. Won, D. Chong, *Bull. Korean Chem. Soc.* **1999**, *20*, 535–538.
- [17] Complex $[\text{MoCp}'_2(\text{OH})(\text{H}_2\text{O})]$ (Cp' = $\eta^5\text{-C}_5\text{H}_4\text{Me}$) was used as catalyst for the selective hydration of several nitriles, in water at 80°C, under neutral conditions (TOF values up to 5 h^{-1}): a) K. L. Breno, M. D. Pluth, D. R. Tyler, *Organometallics* **2003**, *22*, 1203–1211; b) K. L. Breno, M. D. Pluth, C. W. Landorf, D. R. Tyler, *Organometallics* **2004**, *23*, 1738–1746; c) T. J. Ahmed, L. N. Zakharov, D. R. Tyler, *Organometallics* **2007**, *26*, 5179–5187.
- [18] The dimeric nickel species $[\{\text{Ni}(\mu\text{-H})(\text{dippe})\}_2]$ (dippe = 1,2-bis(diisopropylphosphino)ethane) was successfully applied in the selective hydration of acetonitrile, benzonitrile and dicyanobenzenes, in water at 120–180°C, under neutral conditions (TOF values up to 14 h^{-1}): a) M. G. Crestani, A. Arévalo, J. J. García, *Adv. Synth. Catal.* **2006**, *348*, 732–742; b) C. Crisóstomo, M. G. Crestani, J. J. García, *J. Mol. Catal. A* **2007**, *266*, 139–148.
- [19] Catalytic systems composed of $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and a ketoxime were found to catalyze the selective hydration of nitriles, in refluxing water/nitrile 1:1 mixtures, under neutral conditions (TOF values up to 45 h^{-1}): M. N. Kopylovich, V. Yu. Kakushkin, M. Haukka,

- J. J. R. Fraústo da Silva, A. J. L. Pombeiro, *Inorg. Chem.* **2002**, *41*, 4798–4804.
- [20] The heterogeneous system $\text{Ru}(\text{OH})_2/\text{Al}_2\text{O}_3$ was also found to catalyze the selective hydration of nitriles to amides in water at 140 °C (TOF values up to 5 h^{-1}): K. Yamaguchi, M. Matsushita, N. Mizuno, *Angew. Chem.* **2004**, *116*, 1602–1606; *Angew. Chem. Int. Ed.* **2004**, *43*, 1576–1580.
- [21] a) V. Cadierno, S. E. García-Garrido, J. Gimeno, *Chem. Commun.* **2004**, 232–233; b) V. Cadierno, P. Crochet, S. E. García-Garrido, J. Gimeno, *Dalton Trans.* **2004**, 3635–3641; c) V. Cadierno, S. E. García-Garrido, J. Gimeno, N. Nebra, *Chem. Commun.* **2005**, 4086–4088; d) V. Cadierno, S. E. García-Garrido, J. Gimeno, A. Varela-Álvarez, J. A. Sordo, *J. Am. Chem. Soc.* **2006**, *128*, 1360–1370; e) A. E. Díaz-Álvarez, P. Crochet, M. Zablocka, C. Duhayon, V. Cadierno, J. Gimeno, J. P. Majoral, *Adv. Synth. Catal.* **2006**, *348*, 1671–1679; f) V. Cadierno, S. E. García-Garrido, J. Gimeno, *J. Am. Chem. Soc.* **2006**, *128*, 15094–15095; g) V. Cadierno, J. Francos, J. Gimeno, N. Nebra, *Chem. Commun.* **2007**, 2536–2538; h) V. Cadierno, J. Gimeno, N. Nebra, *Chem. Eur. J.* **2007**, *13*, 6590–6594.
- [22] Complexes **2–5** were prepared through conventional routes involving the treatment of the readily available dimeric precursors $[\{\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-arene})\}_2]$ (**1a–d**) with a twofold excess of the appropriate ligand (details and characterization data are given in the Supporting Information).
- [23] Only one further ruthenium catalyst active in aqueous media, namely $[\text{RuH}(\eta^5\text{-C}_9\text{H}_7)(\text{dppm})]$ (dppm = bis(diphenylphosphino)methane), has been reported to date. It was able to catalyze the selective hydration of acetonitrile and benzonitrile at 120 °C using water/nitrile 1:1 mixtures (TOF values not available): W. K. Fung, X. Huang, M. L. Man, S. M. Ng, M. Y. Hung, Z. Lin, C. P. Lau, *J. Am. Chem. Soc.* **2003**, *125*, 11539–11544.
- [24] Attack of water assisted by a nitrogen-containing ligand was already proposed in some nitrile and alkyne hydration studies: a) T. Šmejkal, B. Breit, *Organometallics* **2007**, *26*, 2461–2464; b) D. B. Grotjhan, V. Miranda-Soto, E. J. Kragulj, D. A. Lev, G. Erdogan, X. Zeng, A. L. Cooksy, *J. Am. Chem. Soc.* **2008**, *130*, 20–21, and references cited therein. See also ref. [10].
- [25] a) The ability of the free ligands PTA, PTA-Bn, or DAPTA (5 mol%) to catalyze the hydration of benzonitrile was checked. Thus, after 48 h at 100 °C benzamide was formed in <14% GC yield, confirming that ruthenium species are the real catalysts in this transformation; b) The dimeric precursors $[\{\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-arene})\}_2]$ (**1a–d**) were also by themselves much less efficient than complexes **2,3,4a–d** (up to 82% yield after 24 h at 100 °C; TOF < 1 h^{-1}); c) one referee suggested that HCl, generated in situ from the ruthenium chloride complexes and water, could be responsible of the catalytic activity observed; we have checked that HCl (5 mol%) by itself, or associated with PTA-Bn (5 mol% of each), is completely inoperative in the hydration process (<1% of benzamide is formed after 24 h at 100 °C) discarding this hypothesis.
- [26] For reviews on metal-catalyzed alkyne hydrations, see: a) L. Hintermann, A. Labonne, *Synthesis* **2007**, 1121–1150; b) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3159.
- [27] Microwave-assisted organic synthesis in water has been recently reviewed: D. Dallinger, C. O. Kappe, *Chem. Rev.* **2007**, *107*, 2563–2591.
- [28] We note that these reactions can be performed in a preparative scale and that the catalyst can be recycled. Representative example: 4-Chlorobenzonitrile (2.77 g, 20 mmol), complex **3d** (0.617 g, 1 mmol) and water (40 mL) were introduced, under nitrogen atmosphere, into a Schlenk flask fitted with a condenser. The reaction mixture was stirred at 100 °C until total consumption of the starting material (2 h; GC monitoring). After cooling to room temperature, the solution was set aside at 0 °C (ice bath) for 2 h leading to the selective crystallization of 4-chlorobenzamide, which was separated from the aqueous solution by decantation. Recrystallization from methanol afforded 2.43 g (15.6 mmol) of analytically pure 4-chlorobenzamide (77% yield). To the recovered aqueous solution additional 4-chlorobenzonitrile (20 mmol) was added and the mixture stirred at 100 °C. Almost quantitative conversion of 4-chlorobenzonitrile into 4-chlorobenzamide was observed by GC after 2.5 h.

Received: May 5, 2008

Published online: June 20, 2008