Efficient nitrile hydration mediated by Ru^{II} catalysts in micellar media

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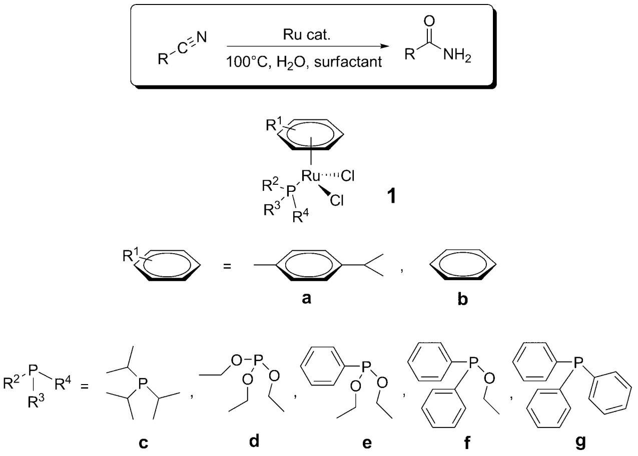
Efficient nitrile hydration to the corresponding amide derivatives is observed in water using poorly soluble [RuCl$_2$(η^6-arene)(PR$_3$)] catalysts 1 with the aid of surfactants to ensure substrate and catalyst solubilization, and enabling ligand effect study on catalytic activity. Amide yields of 40 to 95% can be observed with a variety of aromatic and aliphatic nitriles using the optimized catalyst system, [RuCl$_2$(*p*-cymene)(PPh$_2$OEt)]/Triton X-114. Catalyst separation and recycling is possible.

Chemical transformations, as well as other industrial productive processes, are experiencing a profound transformation to meet sustainability criteria, moving from old methods to new ones developed in agreement with green chemistry principles.[1] Substitution of harmful and hazardous chemicals with others more compatible with human health and the environment is mandatory, with solvent replacement being the first task to be addressed, since amounts of solvents are usually much larger than reagents and products, and their recycling is normally only 50–80% efficient.[2] For this reason, alternative reaction media like ionic liquids, scCO$_2$ and fluorinated solvents, each with its own limitations, have been developed.[3]

Water has been much under-investigated as a solvent for chemical transformations basically because of poor solubility of organic molecules (when these are not polar or endowed with several heteroatoms). However, water is the 'ideal' solvent,[4,5] being economic, non-toxic, non-flammable and, after recovery of contaminants, perfectly compatible with the environment. Substitution of organic solvents with water is desirable,[6] but it becomes especially suited for those chemical transformations in which water is one of the reagents.

This is the case of hydration reactions where addition of water to triple bonds such as alkynes[7] and nitriles provides carbonyl compounds and amides, respectively. Nitrile hydration is an atom-economic reaction and a sustainable method for amide preparation, employed at the industrial level for the production of acrylamide, in the pharmaceutical industry[8] and performed also by nature in the process of nitrile assimilation by enzymes like nitrile hydratases.[9] The reaction between water and the nitrile moiety requires catalytic activation with either Brønsted acids or Lewis acids whose action is to bind the nitrile moiety, which becomes more electrophilic and susceptible to nucleophilic attack by water.[10] The reaction is usually performed under harsh experimental conditions at temperatures close or often above 100 °C – only very recently has an example of a Rh catalyst showing high catalytic activity at room temperature been reported.[11] The most common transition metal catalysts for nitrile hydration are Ni,[12] Pt,[13] Rh,[14] Ir,[8,10] Mo,[15] Au[16] and Ru,[17,18] the latter being by far the most investigated, including the ligand effect[19,20] on catalytic activity. Only recently has organic solvent replacement and use of water as the reaction medium found an application in this process, thanks to either catalyst heterogenization[21] or the use of water-soluble ligands.[14,18] The use of surfactants under micellar conditions is a suitable solution to efficiently overcome issues concerning catalyst as well as substrate solubilization in water, with positive effects on both catalytic activity and selectivity.[22] Aqueous micellar media can convert 'green' a variety of complexes originally developed for work in organic solvents without the need to functionalize a series of ligands with hydrophilic groups to make the corresponding catalysts soluble in water, thus allowing facile catalyst tuning without extra synthetic elaboration.

Herein we report the efficient nitrile hydration mediated by Ru^{II} catalysts of general formula [RuCl$_2$(η^6-Ar)(PR$_3$)] **1** (Scheme 1) bearing a representative range of monophosphines in water in the presence of surfactants at concentrations greatly above the c.m.c. values. Initially, catalyst screening was performed with benzonitrile, using neutral surfactants like TritonX100 and X114 to avoid interfering with ligand substitution. Ru^{II} catalysts bearing electron-rich alkylphosphine **c** showed modest catalytic activity, and the same was observed with the electron-poor triethoxyphosphine ligand **d** (Table 1, entries 1 and 2). Substitution of one ethoxy residue with a phenyl group increased amide formation, and with two aromatic units the highest catalytic activity was observed (Table 1, entries 3 and



Scheme 1 Ru^{II} catalysts **1** used for nitrile hydration in water with surfactants.

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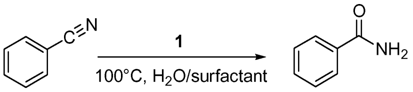
Table 1 Catalyst screening of **1** in the hydration of benzonitrile in water



Entry	Catalyst	Medium	Time (h)	Yield (%)
1	**1ac**	H_2O/TritonX100[b]	20	29
2	**1ad**	H_2O/TritonX100[b]	20	27
3	**1ae**	H_2O/TritonX100[b]	20	37
4	**1ae–Os**[a]	H_2O/TritonX100[b]	20	82
5	**1af**	H_2O/TritonX100[b]	20	93
6	**1ag**	H_2O/TritonX114[c]	20	30
7	**1be**	H_2O/TritonX114[c]	20	5

Experimental conditions: $[Sub]_0$= 0.15 M, 5 mol% **1**, 100 °C, 0.5 mL water. Yield determined by GC analysis.[a] Analogous complex with Os $[OsCl_2(\eta^6\text{-cymene})(PPhOEt_2)]$. [b] Polyoxyethylene(10)isooctyl phenyl ether (150 mM). [c] Polyoxyethylene(8)isooctyl cyclohexyl ether (150 mM).

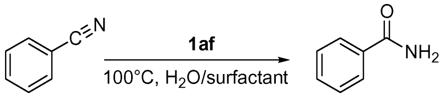
5 respectively). Conversely, triphenylphosphine as ligand led to almost inactive Ru^{II} catalyst (Table 1, entry 6), demonstrating that fine-tuning of both steric and electronic properties is required for good catalytic performance. This catalyst screening can be easily accomplished only in a micellar medium that enables solubilization in water of neutral catalysts with different apolar ligands. It is worth noting that the complex of Os^{II} **1ae** turned out to be more active than the homologous Ru^{II} species (Table 1, entries 3 and 4). As observed with intrinsically water-soluble $[RuCl_2(PR_3^+)(arene)]\ X^-$ species,[18] the η^6-arene residue showed a marked effect on catalytic activity – in fact, substitution of the cymene residue **a** with benzene **b** caused a marked decrease of activity (Table 1, entry 7), probably because of a less labile Ru–arene bond.

With complex **1af** as the best Ru^{II} catalyst at hand, we investigated the nature of the surfactant varying the charge, the length and the kind of functional groups of the tensides employed (Table 2). As shown, even water alone can be used as reaction medium, probably because of partial complex dissolution at 100 °C. Better results are observed with charged anionic, cationic and zwitterionic surfactants (Table 2, entries 2–4) enabling good product formation after 20 h reaction time. Even better performance was possible using neutral surfactants, with amide formation that after 2 h reaction time was >50% with PTS[23] and SPAN60 as surfactants. A further improvement in catalytic activity was achieved with Triton surfactants, in particular X114 (Table 2, entry 8), which gave almost quantitative amide formation in 8 h.

Experimental conditions were investigated in detail (Table 3), and we observed that the best catalyst loading was 2–5 mol% while surfactant concentration screening showed that values above 150 mM influenced negatively the outcome of the reaction. Once we had optimized all these parameters, the substrate scope of the reaction was investigated (Table 4).

Aromatic nitriles reacted readily with catalyst **1af** except electron-poor ones, such as 2-cyanopyridine (Table 4, entry 4). Alkyl nitriles turned out to be suitable substrates, with yields up to 80% depending on the hydrophobic part of the reagent. More hydrophilic substrates bearing alcoholic moieties reacted more slowly, probably because of their higher hydrophilicity that hampered their interaction with the apolar core of the micelles where the catalyst is likely dissolved. In the last column of Table 4 we report also the yields obtained in the absence of surfactant. As can be seen, in most cases either low or no conversions are

Table 2 Surfactant screening in the hydrolysis of benzonitrile with catalyst **1af** in water



Entry	Medium	Time (h)	Yield (%)
1	H_2O	2	11
		20	75
2	H_2O/SDBS[a]	2	36
		20	83
3	H_2O/CTABr[b]	2	44
		20	96
4	H_2O/zwitterionic[c]	2	16
		20	84
5	H_2O/PTS[d]	2	51
		8	90
6	H_2O/SPAN60[e]	2	77
		8	89
7	H_2O/TritonX100[f]	2	58
		8	95
8	H_2O/TritonX114[g]	2	81
		8	97
9	H_2O/TritonX405[h]	2	39
		8	73

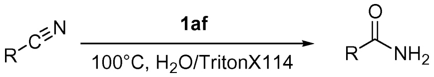
Experimental conditions: $[Sub]_0$= 0.15 M, 5 mol% **1af**, 100 °C, 0.5 mL water. Yield determined by GC analysis.[a] Sodium dodecylbenzene sulfonate (75 mM). [b] Hexadecyl trimethylammonium bromide (75 mM). [c] *N*-Dodecyl-*N*,*N*-dimethyl-3-ammonio-1-propanesulfonate (150 mM). [d] Polyoxyethanyl-α-tocopheryl sebacate (45 mM). [e] Sorbitan monostearate (150 mM). [f] Polyoxyethylene(10)isooctylphenyl ether (150 mM). [g] Polyoxyethylene(8)isooctyl cyclohexyl ether (150 mM). [h] Polyoxyethylene(40)isooctylphenyl ether (150 mM).

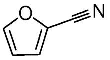
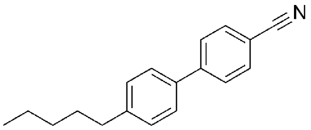
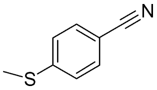
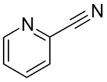
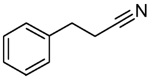
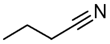
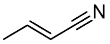
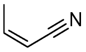
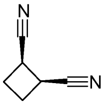
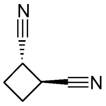
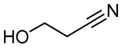
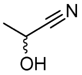
Table 3 Effect of different catalyst loading and surfactant concentration in the hydrolysis of benzonitrile with catalyst **1af** in water

Entry	Catalyst (mol%)	Surfactant (mM)	Time (h)	Yield (%)
1	1	150	2	39
			20	96
2	2	150	2	83
			20	96
3	5	150	2	81
			20	97
4	10	150	2	69
			20	93
5	5	75	2	81
			20	93
6	5	300	2	68
			20	95
7	5	600	2	42
			20	92

Experimental conditions: $[Sub]_0$= 0.15 M, 5 mol% **1af**, 100 °C, 0.5 mL water. Yield determined by GC analysis.

Table 4 Substrate scope of the nitrile hydration reaction with catalyst **1af**



Entry	Substrate	Time (h)	Yield (%)	Yield in H_2O (%)
1		12	95	0
2		24	89	0
3		24	90	5
4		24	10	0
5		24	80[a]	11
6		7	77	11
7	 56%  44%	24	72[b]	21[b]
8	 45%  55%	24	41[b]	79[b]
9		24	50	45[c]
10		24	14	10

Experimental conditions: $[Sub]_0$= 0.15 M, 5 mol% **1af**, 100 °C, [TritonX114] = 150 mM, 0.5 mL water. Yield determined by GC analysis.[a] 6% acid formation. [b] Sum of isomers. [c] 10% acid formation.

observed, providing evidence for the fundamental role of the surfactant in bringing catalyst and reactants into contact.

However, when the nitrile becomes more hydrophilic (entries 8–10) its solubility in water at 100 °C is likely to be high, helping the dissolution of an appreciable amount of water-insoluble catalyst. This is why for hydrophilic nitriles some activity is observed, in some cases comparable to the micellar system.

An important issue with these systems is the possibility to separate and recycle the catalyst. A preliminary experiment was carried out by adding a further 1 mmol of benzonitrile at the end of the experiment reported in Table 2, entry 8, to check whether the catalyst was still active. A further 30% conversion of benzonitrile in benzamide was observed after 30 h. This lower conversion can be due to both a dilution effect and to competition between benzonitrile and benzamide for coordination to the metal. Using the experimental conditions reported in Table 2 (substrate 1 mmol), we then attempted to optimize catalyst recycling using neutral TritonX114 surfactant. Under these conditions phase separation is virtually impossible because of emulsion formation when the organic solvent (necessary for separating the catalyst from the organic products) is added. CTABr was then checked as a charged surfactant in order to minimize its solubilization in organic media. Chloroform was used for extraction, and we observed dissolution in the organic phase of the Ru^{II} species (as confirmed by green color transfer from the micellar phase to the chlorinated phase) while the surfactant and the benzamide remained dispersed in water. Amide product could be precipitated by diluting the aqueous solution (20 times) and cooling the system to 5 °C. The catalyst was thus isolated by organic solvent evaporation, and to this, water, CTABr and nitrile substrate were added for the recycling experiments. The reaction led to 95% yield in benzamide in the first cycle, 81% in the second followed by a decrease of catalytic activity in the third cycle, where the yield was 54%. This loss of activity is probably due to incomplete recovery of the catalyst during work-up. GC-MS analysis on the first extracted organic phase showed the presence of *p*-cymene, suggesting that the active catalytic species lacks this aromatic ligand, which is probably displaced by the incoming nitrile moiety.

Summarizing the results reported in this paper, complex **1af** (5 mol%) associated with TritonX114 provides good yields for amide formation from a representative range of substrates at 100 °C, demonstrating comparable catalytic activity to intrinsically water-soluble Ru^{II} catalysts bearing hydrophilic ligands.[18]

In conclusion, we have demonstrated that micelles represent suitable media for reactions involving water as a reagent, such as nitrile hydration catalyzed by Ru^{II} species **1**. Neutral surfactants showed the best catalytic activity, probably because they do not interfere (as charged species do) with ligand exchange on the catalyst, enabling almost quantitative hydration on benzonitrile. With respect to the use of intrinsically water-soluble catalysts, micellar media represent an alternative approach to solubilize hydrophobic complexes in water, and allow the facile screening of different catalysts without the need for elaborate ligand modification, but with a less straightforward separation and recycling. Specifically, this reaction medium enabled the screening of common monophosphine ligands, with the observation being made that neither electron-rich nor electron-poor phosphines ensured high catalytic activity, but rather an appropriate balance of steric and electronic features are required.

Catalysis in water offers wide opportunities and deserves deep investigation, since positive results are still largely unpredictable. On the other hand, the use of water as the solvent is a strong argument in 'going green'. The micellar approach can, in principle, be applied to exploit libraries of existing catalysts for libraries of reactions without the need to synthesize a specific water-soluble catalyst for each reaction.

Experimental section

General

^1H NMR, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded at 298 K, unless otherwise stated, on a Bruker AVANCE 300 spectrometer operating at 300.15, 75.5, 121.50 MHz, respectively. δ values in ppm are relative to $SiMe_4$ for ^1H and ^{13}C and 85% H_3PO_4 for ^{31}P. All reactions were monitored by GC analysis. GLC measurements were taken on a Hewlett-Packard 6890A gas chromatograph equipped with a FID detector (carrier gas He) and 25 m HP-5 column T_{inj} 280 °C, T_{det} 300 °C, 100 °C for 5 min, 10 °C/min to 200 °C. GC-MS analysis was performed on a quadrupole Trace GC 2000 ThermoFinnigan instrument equipped with a 30 m HP-5MS column (carrier gas He). Ru^{II} complexes were prepared according to a general method reported in the literature[24] and were a generous gift of Professors G. Albertin and S. Antoniutti of this university. Nitriles and surfactants are all commercially available products and were used as received. The identities of the amide products were assessed by comparison of their ^1H, ^{13}C and GC-MS spectra.

General procedure for the catalytic reactions

The Ru^{II} catalysts **1** (7.5 mM, 5 mol% of Ru), water (0.5 mL), the appropriate amount of surfactant and the corresponding nitrile (0.15 M, 75 μmol) were introduced to a vial equipped with a screw-capped septum. The reaction mixture was stirred at 100 °C for the time required. The course of the reaction was monitored by regular sampling of aliquots of the solution, followed by dilution with MeOH and analysis by GC. Quenching of the reaction was found to be unnecessary. Catalyst recycle experiments were performed on 1 mmol amount of benzonitrile using CTABr as surfactant following the experimental conditions reported in Table 2.

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References

1 P. Anastas and J. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.
2 R. A. Sheldon, *Green Chem.*, 2005, **7**, 267.
3 (*a*) D. J. Adams, P. J. Dyson, S. J. Tavener, *Chemistry in Alternative Reaction Media*, Wiley, 2004; (*b*) S. Liu and J. Xiao, *J. Mol. Catal. A: Chem.*, 2007, **270**, 1; (*c*) C. Reichardt, *Org. Process Res. Dev.*, 2007, **11**, 105.
4 (*a*) U. M. Lindström, *Organic Reactions in Water*, Blackwell, Oxford, 2007; (*b*) C. J. Li, *Chem. Rev.*, 1993, **93**, 2023; (*c*) C. J. Li, *Chem. Rev.*, 2005, **105**, 3095.
5 For 'on-water' conditions, see: A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725.
6 H. C. Hailes, *Org. Process Res. Dev.*, 2007, **11**, 114.
7 L. Chen and C.-J. Li, *Adv. Synth. Catal.*, 2006, **348**, 1459.
8 V. Y. Kukushkin and A. J. L. Pombeiro, *Chem. Rev.*, 2002, **102**, 1771.
9 P. K. Mascharak, *Coord. Chem. Rev.*, 2002, **225**, 201.
10 For a review of the reaction see: V. Y. Kukushkin and A. J. L. Pombeiro, *Inorg. Chim. Acta*, 2005, **358**, 1.
11 A. Goto, K. Endo and S. Saito, *Angew. Chem., Int. Ed.*, 2008, **47**, 3607.
12 M. G. Crestani and J. J. García, *J. Mol. Catal. A: Chem.*, 2009, **299**, 26.
13 (*a*) T. Ghaffar and A. W. Parkins, *J. Mol. Catal. A: Chem.*, 2000, **160**, 249; (*b*) X. Jiang, A. J. Minnaard, B. L. Feringa and J. G. de Vries, *J. Org. Chem.*, 2004, **69**, 2327; (*c*) T. J. Ahmed, B. R. Fox, S. M. M. Knapp, R. B. Yelle, J. J. Juliette and D. R. Tyler, *Inorg. Chem.*, 2009, **48**, 7828.
14 M. C. Koffi-Bie Djoman and A. N. Ajjou, *Tetrahedron Lett.*, 2000, **41**, 4845.
15 K. L. Breno, M. D. Pluth and D. R. Tyler, *Organometallics*, 2003, **22**, 1203.
16 R. S. Ramón, N. Marion and S. P. Nolan, *Chem. Eur. J.*, 2009, **15**, 8695.
17 (*a*) S. I. Murahashi, S. Sasao, E. Saito and T. Naota, *J. Org. Chem.*, 1992, **57**, 2521; (*b*) T. Smejkal and B. Breit, *Organometallics*, 2007, **26**, 2461; (*c*) C. W. Leung, W. Zheng, Z. Zhou, Z. Lin and C. Po Lau, *Organometallics*, 2008, **27**, 4957; (*d*) C. S. Yi, T. N. Zeczycki and S. V. Lindeman, *Organometallics*, 2008, **27**, 2030.

18 V. Cadierno, J. Francos and J. Gimeno, *Chem. Eur. J.*, 2008, **14**, 6601.

19 W. K. Fung, X. Huang, M. L. Man, S. M. Ng, M. Y. Hung, Z. Lin and C. Po Lau, *J. Am. Chem. Soc.*, 2003, **125**, 11539.

20 T. Oshiki, H. Yamashita, K. Sawada, M. Utsunomiya, K. Takahashi and K. Takai, *Organometallics*, 2005, **24**, 6287.

21 V. Polshettiwar and R. S. Varma, *Chem. Eur. J.*, 2009, **15**, 1582.

22 (*a*) U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751; (*b*) T. Dwars, E. Paetzold and G. Oehme, *Angew. Chem., Int. Ed.*, 2005, **44**, 7174; (*c*) J. Zhang, X.-G. Meng, X.-C. Zeng and X.-Q. Yu, *Coord. Chem. Rev.*, 2009, **253**, 2166.

23 B. H. Lipshutz and S. Ghorai, *Aldrichimica Acta*, 2008, **41**, 59.

24 (*a*) B. Therrien, *Coord. Chem. Rev.*, 2009, **253**, 493; (*b*) E. Hodson and S. J. Simpson, *Polyhedron*, 2004, **23**, 2695.