Arene-ruthenium(II) and osmium(II) complexes as catalysts for nitrile hydration and aldoxime rearrangement reactions

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Dedicated to Prof. Maurizio Peruzzini on the occasion of his 65th birthday and in recognition to his outstanding achievements in Organometallic Chemistry

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Abstract

The catalytic hydration of nitriles and the rearrangement of aldoximes are atom-economical routes to generate primary amides of great academic and industrial interest. Among the different families of catalysts that have been developed for these transformations, the most extensively studied is that of (η^6-arene)-ruthenium(II) derivatives since, by appropriate selection of the auxiliary ligands, high activities and selectivities can be reached under remarkably mild conditions. Very recently, some examples of (η^6-arene)-osmium(II) complexes able to hydrate nitriles with effectiveness comparable or even superior to that of their ruthenium analogues have also appeared. In this short review a survey of this chemistry is presented.

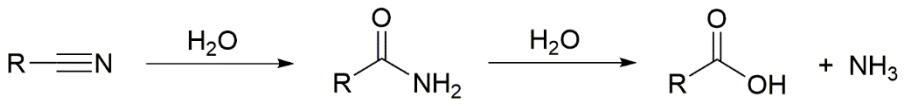
Keywords: Ruthenium; Osmium; Half-sandwich complexes; Homogeneous Catalysis; Hydration of nitriles; Rearrangement of aldoximes.

Highlights:

- Arene-Ru(II) and Os(II) catalysts in nitrile hydration reactions are reviewed.
- Their involvement in the catalytic rearrangement of aldoximes is discussed.
- Procedures for the direct conversion of aldehydes into primary amides are also covered.

1. Introduction

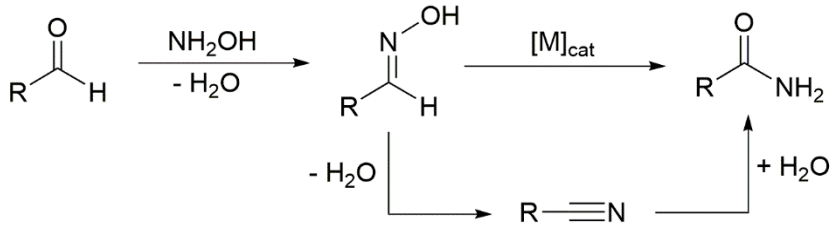
Since the pioneering work of Winkhaus and Singer in 1967 [1], and the early contributions by the groups of Ogata [2], Baird [3] and Bennett [4], the chemistry of half-sandwich (η^6-arene)-ruthenium(II) complexes has grown exponentially, representing nowadays one of the most versatile and widely studied families of organometallic ruthenium compounds [5-12]. The high structural diversity and the fine tuning of the stereo-electronic properties of the metal center that can be achieved within this family of complexes, along with their easy access and handle, have enabled their application in different fields including medicinal [13-19], supramolecular chemistry [20-24] and homogeneous catalysis [25-30]. Unlike many organometallic compounds, the arene-ruthenium complexes have a remarkable stability against water, property that our research group and others have exploited in recent years for the development of efficient catalysts for nitrile hydration reactions (Scheme 1). The catalytic hydration of nitriles is a relevant transformation in both academia and industry because the primary amide products are versatile synthetic intermediates, as well as useful building blocks for the manufacture of pharmaceutical molecules and engineering polymers [31,32]. The use of metal catalysts to promote the process is particularly advantageous compared to more classical methodologies involving strong Brønsted acids or bases, since it allows working under milder conditions, with an increased functional group compatibility, and avoiding the over-hydrolysis of the amide products (see Scheme 1). In addition, compared to enzymatic procedures [33-35], they require an easier handling, are generally cheaper, and provide a wider substrate scope. All these advantages have motivated multitude of studies in the field and a huge number of catalysts featuring metals of all the transition series can be currently found in the literature [36-44]. Among them, those involving ruthenium are probably the most abundant, with the arene-ruthenium(II) derivatives playing a central role.



Scheme 1. The nitrile hydration and amide hydrolysis reactions.

An alternative procedure to access primary amides in an atom-economical manner is the metal-catalyzed rearrangement of aldoximes, a process that formally involves the initial dehydration of the substrate into the corresponding nitrile, which is subsequently

rehydrated (Scheme 2) [42,45-47]. This type of amide bond forming reactions has attracted great interest in recent years mainly due to the availability of the starting materials, which are easily accessible by condensation of an aldehyde with hydroxylamine. Indeed, protocols for the direct aldehyde-to-primary amide conversion, via *in situ* generation of an aldoxime intermediate, are known [42,45-47]. As in the hydration of nitriles, works by our research group and others have demonstrated the enormous potential offered by arene-ruthenium(II) complexes to promote these transformations in a selective manner.



Scheme 2. Formation and catalytic rearrangement of aldoximes.

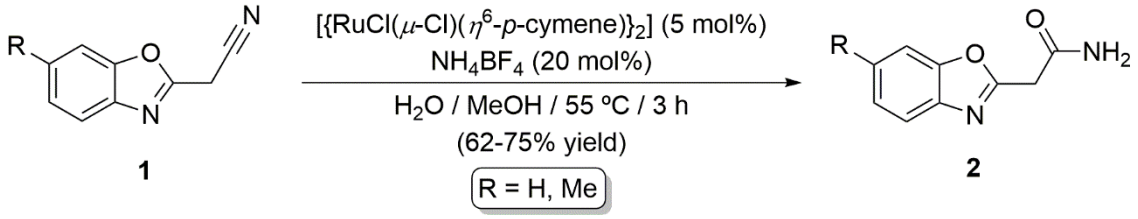
In this short review, a comprehensive overview of the application of (η^6-arene)-ruthenium(II) complexes as catalysts in both nitrile hydration and aldoxime rearrangement reactions is given. Examples of (η^6-arene)-osmium(II)-based catalysts are also discussed since very recent results have shown that the activity featured by some representatives in the hydration of organonitriles can outperform that of their ruthenium analogues.

2. Nitriles hydration reactions

2.1. Arene-ruthenium(II) catalysts

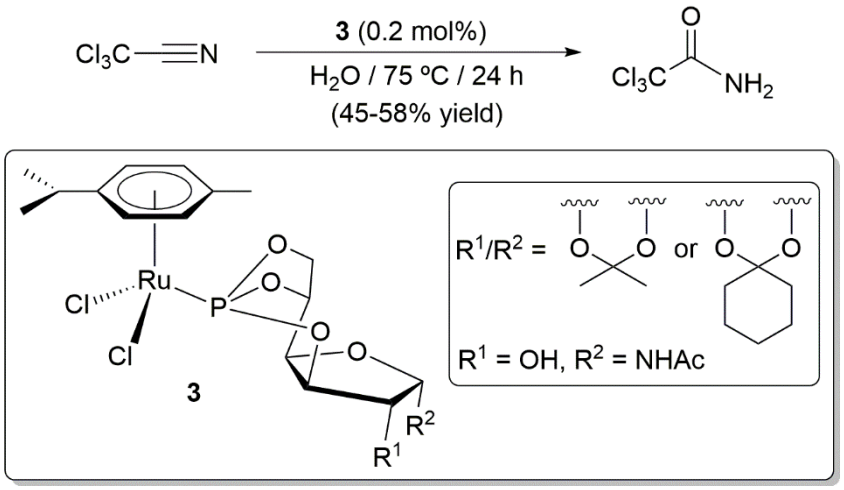
The chloride-bridged dimers [{RuCl(μ-Cl)(η^6-arene)}$_2$] are the most common precursors in the chemistry of arene-ruthenium(II) complexes [5-12]. Although by themselves these species are capable of catalyzing the hydration of C≡N bonds [48], their activity is not very high and their use has not been widespread. In this context, from a synthetic point of view, the most remarkable result is probably the one published by Dixneuf and co-workers and depicted in Scheme 3, which allowed the access under mild conditions to a couple of benzoxazolylacetamides **2** by hydration of the corresponding

benzoxazolylacetonitriles **1** employing [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] as the catalyst in combination with the chloride abstractor NH_4BF_4 [49].



Scheme 3. Hydration of benzoxazolylacetonitriles **1** employing dimer [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$].

Mononuclear complexes featuring *P*-donor ligands, *i.e.* compounds of type [$RuCl_2$(η^6-arene)(PR_3)], are undoubtedly the catalytic systems more widely studied to date. In this regard, the first work quoted in the literature was reported by Nazarov, Hartinger and co-workers in 2008, who used the phosphite-derivatized ruthenium-carbohydrate complexes **3** to promote the hydration of trichloroacetonitrile [50]. As shown in Scheme 4, performing the reactions directly in water at 75 ºC with 0.2 mol% of these complexes, the desired trichloroacetamide product was obtained in moderate yield after 24 h (TOF up to 12 h^{-1}) and with a selectivity of 96-98% (the formation of minor amounts of ammonium trichloroacetate was in all the cases observed).



Scheme 4. Hydration of trichloroacetonitrile using the phosphite-ruthenium(II) complexes **3**.

Almost simultaneously, in our group we investigated the catalytic behaviour of a series of mononuclear complexes [$RuCl_2$(η^6-arene)(PR_3)] (arene = benzene, *p*-cymene,

mesitylene, hexamethylbenzene (hmb)) containing the water-soluble phosphine ligands TPPMS, PTA, PTA-Bn and DAPTA (see Fig. 1) [48].

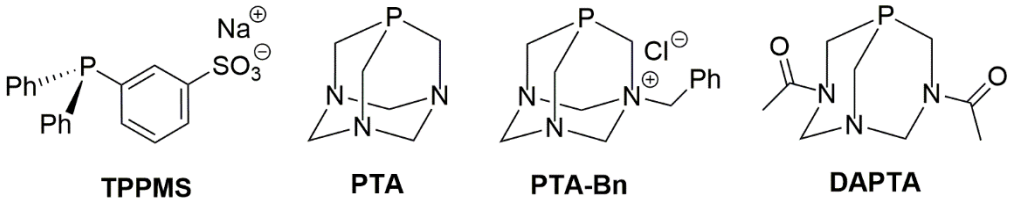
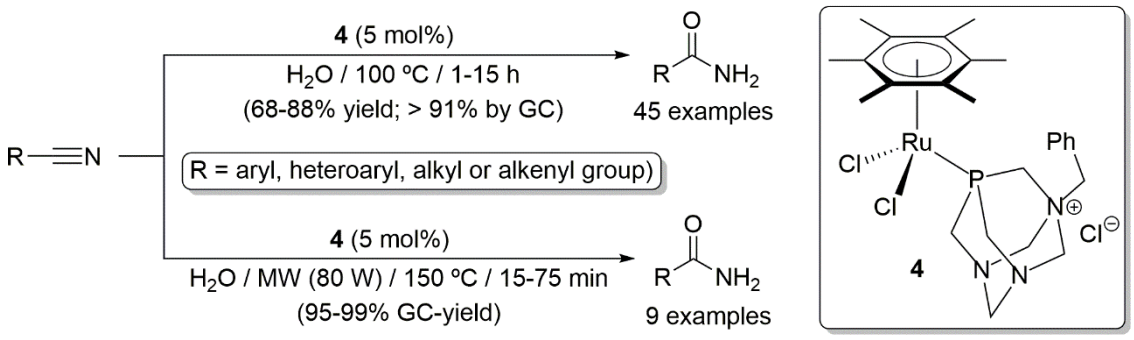


Fig. 1. Structure of the water-soluble phosphine ligands TPPMS, PTA, PTA-Bn and DAPTA.

All of them proved to be active in the hydration of the model benzonitrile substrate at 100 ºC employing water as the only solvent, a metal loading of 5 mol%, and in the absence of additives [51]. However, the nature of both the phosphine and arene ligand played a crucial role on the efficiency of the process. Thus, with the regard to the arene, the rate order observed was hmb > mesitylene > *p*-cymene > benzene regardless of the phosphine employed. Taking into account that dissociation of one of the chloride ligands is required to generate a vacant site on the metal for the coordination of the nitrile, it is not surprising that those compounds containing the more electron-rich and sterically demanding arene, *i.e.* hmb, led to the best results. Regarding the phosphines, those complexes containing the nitrogen-containing cage-like ligands PTA, PTA-Bn and DAPTA resulted more effective than their analogues with the sulfonated triphenylphosphine TPPMS (TOF = 1.0-9.9 h^{-1} *vs* 0.2-0.4 h^{-1}). Among them, the best performance was provided by [$RuCl_2$(η^6-hmb)(PTA-Bn)] (**4**), which led to the quantitative formation of benzamide after only 2 h of heating (TOF = 9.9 h^{-1}). Moreover, the generality of the process and the exquisite functional group compatibility of complex **4** was confirmed for a large number of functionalized benzonitriles, as well as different heteroaromatic, aliphatic and α,β-unsaturated nitriles (Scheme 5). Turnover frequencies (TOF) in the range of 1.3-19.6 h^{-1} were achieved in these reactions, values that could be increased up to 126.7 h^{-1} carrying out the reactions at 150 ºC under microwave (MW) irradiation [48]. Also of note is the fact that, after selective crystallization of the amide product, the reuse in a second catalytic reaction of the aqueous solution containing complex **4** could be demonstrated. At this point it should be mentioned that comparable results in terms of activity were obtained by Scarso, Strukul and co-workers with compounds [$RuCl_2$(η^6-*p*-cymene)(PR_3)] (PR_3 = PPh_3, P^iPr_3, PPh_2OEt, $PPh(OEt)_2$,

$P(OEt)_3$) under micellar conditions [52]. Among them, [$RuCl_2(\eta^6$-*p*-cymene){$PPh(OEt)_2$}] proved to be the most effective. Thus, using 5 mol% of this complex, several aromatic and aliphatic nitriles were converted into the corresponding primary amides in moderate to high yields (40-95%) after 7-24 h of heating at 100 ºC in a water/Triton X-114 mixture (TOF up to 5 h^{-1}). In addition, catalyst separation and recycling was also possible in this case (three consecutive runs).



Scheme 5. Nitrile hydration reactions with the water-soluble complex [$RuCl_2(\eta^6$-hmb)(PTA-Bn)] (**4**).

On the other hand, it is also worth mentioning that complex [$RuCl_2(\eta^6$-hmb)(PTA-Bn)] (**4**) is capable to catalyze the hydration of organonitriles employing as solvent glycerol, a byproduct of the biodiesel industry that has gained interest as a biodegradable reaction medium for synthetic organic chemistry in recent years [53-57], although compared to the aqueous conditions commented above, longer reaction times and a higher temperature (160 ºC) were in this case needed to attain good conversions [58]. After extraction of the amide product formed with ethyl acetate, the glycerol phase containing **4** could also be successfully reused in a second catalytic cycle. In this context, in order to improve the recyclability of this type of catalysts, we also developed in collaboration with Basset and Polshettiwar a heterogeneous system by supporting a *p*-cymene-ruthenium-PTA complex on the surface of silica-coated ferrite nanoparticles (**5** in Fig. 2) [59]. Turnover frequencies of up to 126 h^{-1} were achieved with **5** working in pure water at 150 ºC under MWs irradiation, its paramagnetic nature allowing an easy separation from the aqueous solution containing the amides with the help of an external magnet. The recovered catalyst could be recycled up to six times leading to cumulative turnover numbers (TON) of 304-358. Similarly to [$RuCl_2(\eta^6$-hmb)(PTA-Bn)] (**4**), the nanocatalyst **5** featured a broad substrate scope and functional group compatibility. In addition, just by adjusting the time of irradiation, the conversion of different dinitriles into the

corresponding mono- and dicarboxamides could be achieved with a selectivity that has been rarely documented in the literature (two representative examples are given in Scheme 6) [60].

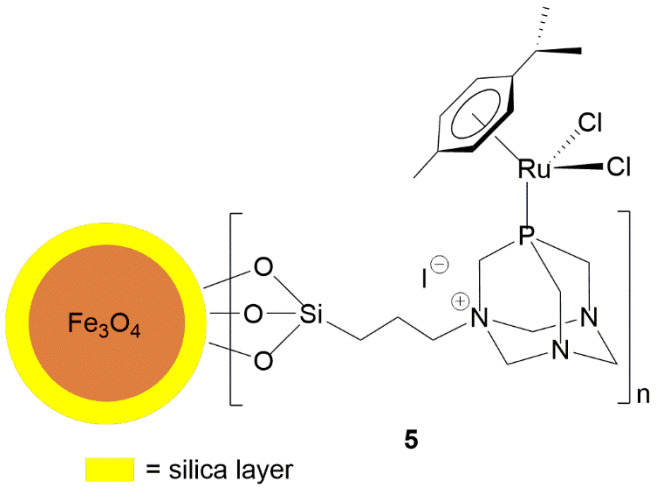
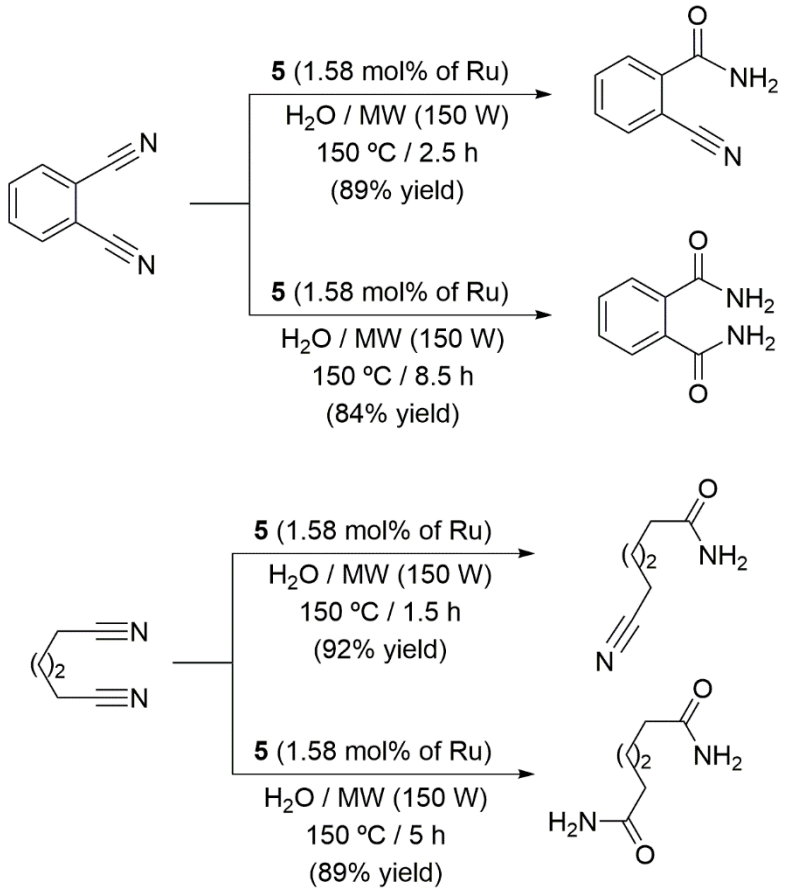


Fig. 2. Structure of the ruthenium nanocatalyst **5**.



Scheme 6. Selective mono- and dihydration of dinitriles employing the nanocatalyst **5**.

In addition to the systems just discussed, other water-soluble ruthenium catalysts containing PTA-type ligands have been described in the literature [61], including the (η^6-toluene)-ruthenium(II) derivatives **6** [62] and **7** [63] developed by Frost and co-workers (Fig. 3). Both complexes are able to promote the hydration process in pure water at 100 ^{o}C under aerobic conditions, showing activities comparable to that of [$RuCl_2$(η^6-hmb)(PTA-Bn)] (**4**) when faced with aromatic nitriles. However, their effectiveness significantly decreased when pyridyl or aliphatic nitriles were employed as substrates, and they led to mixtures of products starting from α,β-unsaturated nitriles. It is also worth mentioning at this point that Frost and co-workers studied in depth the lifetime and activity of complex **6** using the hydration of benzonitrile into benzamide as model, observing an interesting TOF increase as the catalyst loading was reduced. In particular, using only 0.001 mol% of **6**, TON and TOF values of 97000 and 285 h^{-1} could be attained with a 97% conversion after 14 days, a result that reveals the exacerbated stability of this catalyst in aqueous solution.

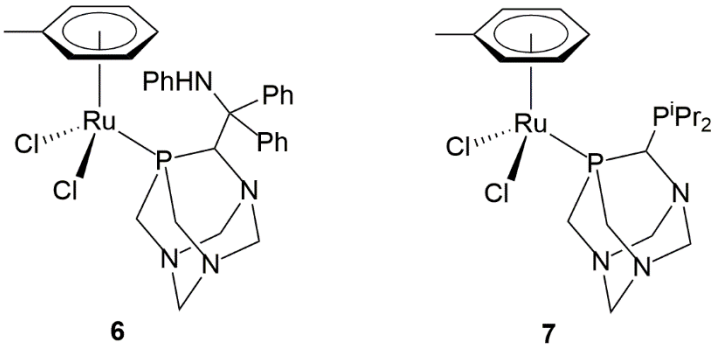
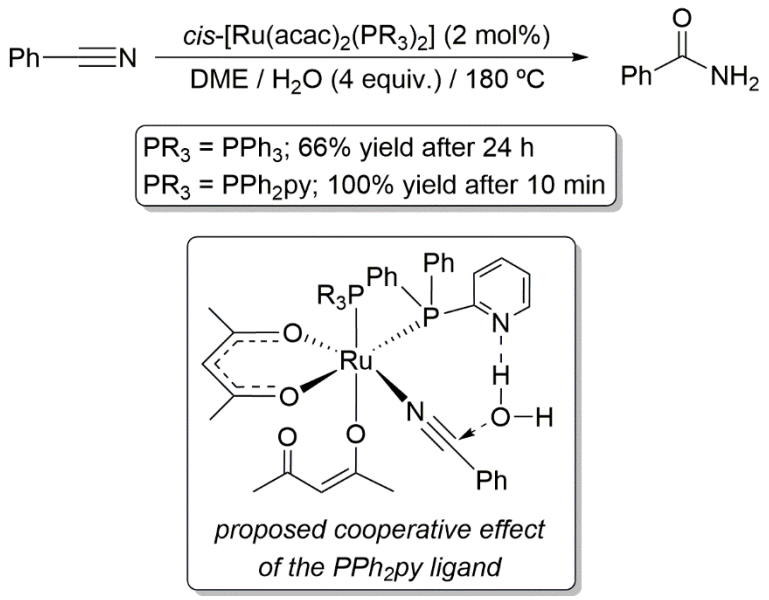


Fig. 3. Structure of the (η^6-toluene)ruthenium(II) complexes **6** and **7**.

Although no experimental or theoretical evidences have been given, the good results obtained with all these complexes could be associated with a potential cooperative effect of the PTA-based ligands which, due to the presence of N atoms on their skeletons, can interact with water molecules by hydrogen bonding, thus facilitating their approach and attack to the nitrile once coordinated to the metal center. Such a cooperative effect of the ligands was proposed for the first time by Oshiki and co-workers to explain the marked differences in reactivity observed between the octahedral Ru(II) complexes *cis*-[$Ru(acac)_2(PPh_3)_2$] (acac = acetylacetonate) and *cis*-[$Ru(acac)_2(PPh_2py)_2$] (PPh_2Py = 2-(diphenylphosphino)pyridine) in related nitrile hydration processes (an illustrative example is given in Scheme 7) [64].



Scheme 7. Hydration of benzonitrile catalysed by complexes *cis*-[Ru(acac)$_2$(PR$_3$)$_2$].

Inspired by this Oshiki's work, our group synthesized and studied the catalytic behaviour of a series of arene-ruthenium(II) complexes with different pyridyl-phosphine ligands, *i.e.* compounds **8-10** in Fig. 4 [65]. The results obtained were not as expected, observing very modest activities (comparable to those of related compounds featuring the non-cooperative triphenylphosphine ligand [RuCl$_2$(η^6-arene)(PPh$_3$)]) in the hydration of the benzonitrile model substrate (TOF < 1 h^{-1} at 100 ºC). In the case of compounds **8** and **9** the low catalytic activities found were associated with the marked tendency of the ligands to adopt a chelating κ^2-(*P*,*N*)-coordination in solution, as assessed by NMR spectroscopy and catalytic experiments carried out with the corresponding cationic species [RuCl$_2$(η^6-arene){κ^2-(*P*,*N*)-PR$_3$}][SbF$_6$] (PR$_3$ = PPh$_2$py, PPh$_2$(py-4-NMe$_2$)). Unlike **8** and **9**, the presence of a bulky *tert*-amyl substituent adjacent to the nitrogen atom of the pyridyl ring in complexes **10** prevents the chelation of the ligand in solution from occurring, the low effectiveness shown by these complexes being probably related, in this case, to the lability of the ligand. Indeed, in a later work we found that, due to steric constraints, it can be easily displaced from the metal even by weak two-electron donor ligands such as SMe$_2$ [66]. We must mention at this point that modest results were also obtained by the groups of Lammertsma [67] and Jessop [68] when studying the hydration of benzonitrile with catalytic systems based on the *in situ* combination of dimer [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] and the related 1,3-*P*,*N*-donor ligands Ar$_2$PC(Ar´)=NR (Ar/Ar´ =

Ph, 4-C_6H_4Me, 4-$C_6H_4CF_3$; R = Me, ^iPr; TOF < 1 h^{-1} at 100 ºC or up to 19 h^{-1} at 180 ºC) and $Ph_2PC(NMe_2)=N^iPr$ (TOF < 1 h^{-1} at 180 ºC), respectively.

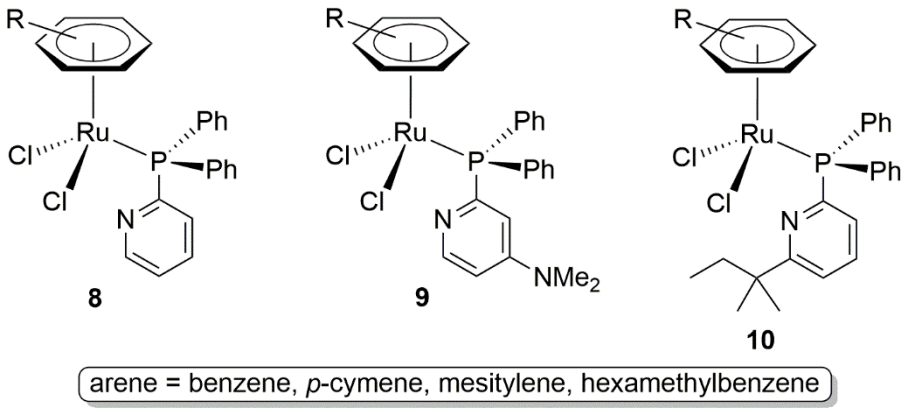


Fig. 4. Structure of the arene-ruthenium complexes **8-10** containing pyridyl-phosphine ligands.

With the idea of exploring possible cooperative effects of the ligands, our group also synthesized different arene-ruthenium(II) complexes **11-13** with potentially H-bond accepting amino-aryl-phosphines (Fig. 5) [69]. We reasoned that the activity of these complexes would be strongly dependent on the exact location of the potentially cooperative amino group on the aromatic ring, expecting that those complexes substituted in *ortho* position would be much more effective than their *meta*- or *para*-substituted counterparts.

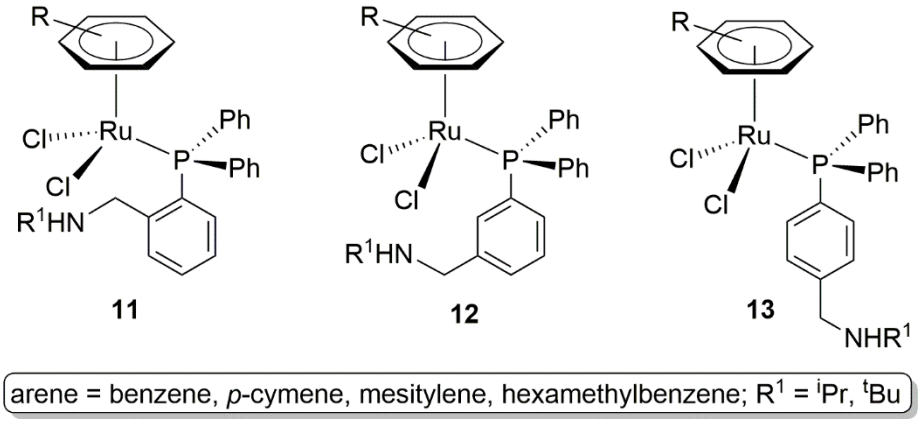


Fig. 5. Structure of the arene-ruthenium complexes **11-13** containing amino-aryl-phosphine ligands.

Contrary to our expectations, the differences in catalytic activity found between the three series of complexes were negligible with TOF values in the range 1-3 h^{-1} for the hydration of the model benzonitrile substrate (reactions performed in water at 100 ºC with

metal loadings of 5 mol%). However, it should be noted that the presence of the amino groups led now to a slight improvement in catalytic activity compared to that observed with the corresponding non-functionalized species [$RuCl_2(\eta^6$-arene)(PPh_3)] (TOF < 0.1 h^{-1} under identical reaction conditions). These observations, along with the fact that the reaction rates in the hydration of benzonitrile by complexes [$RuCl_2(\eta^6$-arene)(PPh_3)] is enhanced when the catalytic reactions are carried out in the presence of free $PhCH_2NH^iPr$ or $PhCH_2NH^tBu$, amines that mimic the substituents present on the *P*-donor ligands of compounds **11-13**, suggest the participation of the amino-substituted ligands of **11-13** as internal Brønsted bases during catalysis. In this way, they would generate the more nucleophilic OH^- species in the medium, whose attack to the coordinated nitrile would be favoured (see Fig. 6).

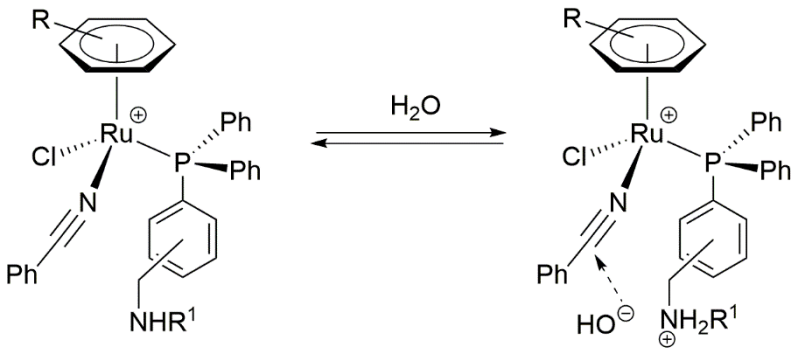
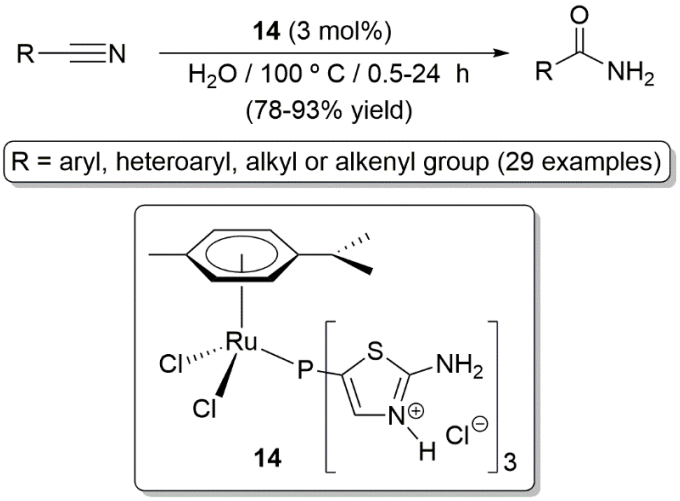


Fig. 6. Proposed effect of amino-aryl-phosphine ligands in complexes **11-13** during catalysis.

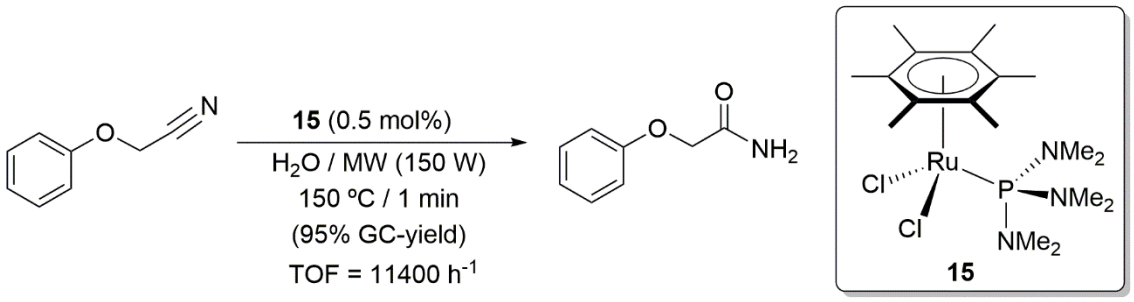
Results obtained by our group in collaboration with that of Majoral demonstrated the higher effectiveness as auxiliary ligands of thiazolyl-phosphines in comparison with the pyridyl- and amino-aryl-phosphines just commented [70]. For example, employing a 3 mol% of the (*p*-cymene)Ru(II) complex **14**, we were able to hydrate a large variety of aromatic, heteroaromatic, aliphatic and *α,β*-unsaturated nitriles in high yields and short times performing the catalytic reactions in pure water at 100 ºC (TOF up to 66 h^{-1}) (see Scheme 8). In addition, an unusually high TON value of 9800 could be attained in the hydration of benzonitrile employing a metal loading of only 0.01 mol%, reaction which led to the desired benzamide in 98% GC-yield after 7 days. This result demonstrates the high robustness of complex **14**. An additional remarkable aspect of this catalyst, for which we suspected a possible cooperative effect of the heteroatoms present in the ligand skeleton, is that its high solubility in water enabled its recycling (up to five consecutive

runs; separation of the amide product by selective crystallization from the aqueous solution).

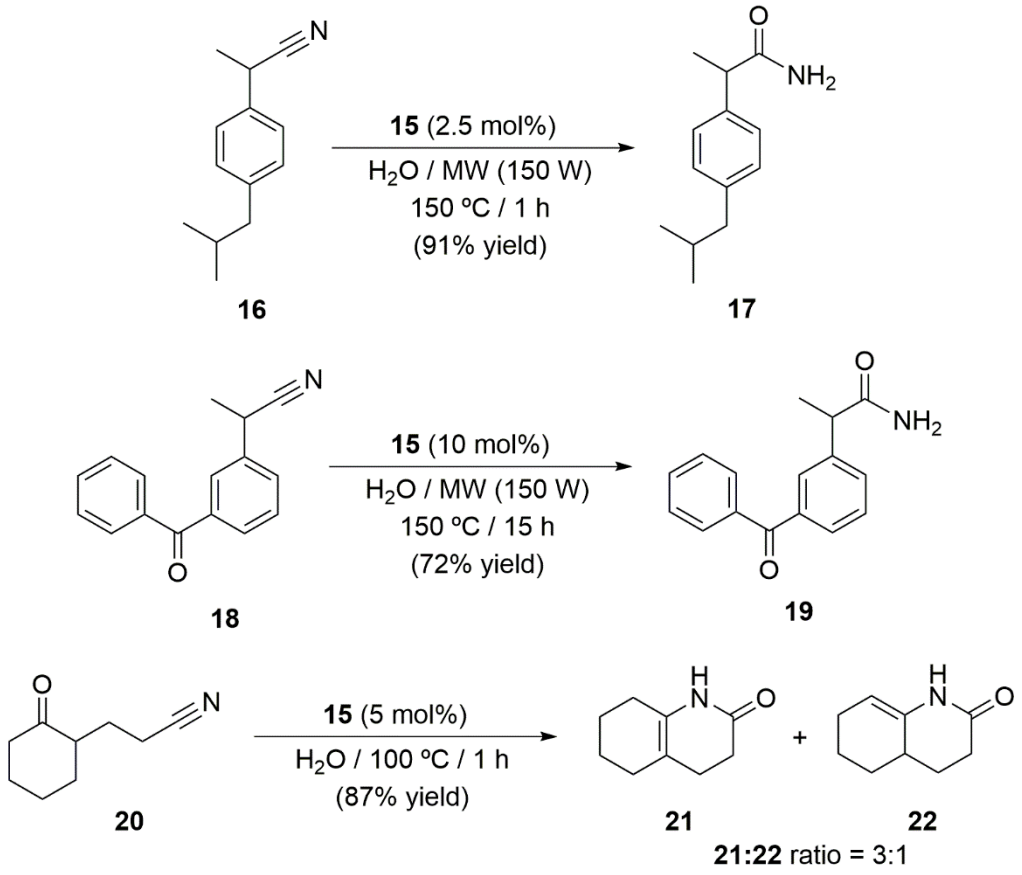


Scheme 8. Nitrile hydration reactions catalyzed by the water-soluble ruthenium(II) complex **14**.

Another relevant family of auxiliary *P*-donor ligands in metal-catalyzed nitrile hydration reactions is that of amino-phosphines $P(NR_2)_3$ [71]. In this context, we reported in 2011 the preparation of several arene-ruthenium(II) complexes containing commercially available tris(dimethylamino)phosphine, *i.e.* compounds $[RuCl_2(\eta^6\text{-arene})\{P(NMe_2)_3\}]$ (arene = benzene, toluene, *p*-cymene, mesitylene, hmb), which are also capable to promote nitrile hydration reactions in pure water and in the absence of additives [72]. Among them, complex $[RuCl_2(\eta^6\text{-hmb})\{P(NMe_2)_3\}]$ (**15**) containing again the more sterically demanding and electron-rich arene offered the best results in terms of activity, being able to hydrate a large variety of aromatic and aliphatic organonitriles (34 examples) in high yields and short times (from 5 min to 5 h), at 100 ºC, with a ruthenium loading of 5 mol%. Under these conditions, turnover frequencies of up to 594 h^{-1} were reached, value that could be increased to 11400 h^{-1} when the hydration of phenoxyacetonitrile was performed at 150 ºC with 0.5 mol% of **15** using MWs as the heating source (see Scheme 9). In addition, we demonstrated the synthetic utility of complex **15** with the high yield access to the nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofenamide (**17**) and ketoprofenamide (**19**) by hydration of the respective organonitriles **16** and **18** [72,73], as well as with the conversion of the δ-ketonitrile **20** into the isomeric ene-lactams **21** and **22** through a tandem hydration/cyclocondensation sequence (Scheme 10) [72].



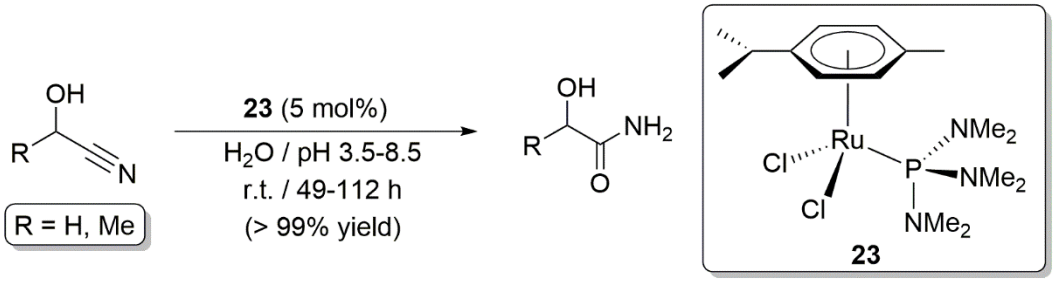
Scheme 9. Hydration of phenoxyacetonitrile employing [$RuCl_2(\eta^6$-hmb){$P(NMe_2)_3$}] (**15**) as catalyst under MW irradiation.



Scheme 10. Access to ibuprofenamide, ketoprofenamide and ene-lactams using [$RuCl_2(\eta^6$-hmb){$P(NMe_2)_3$}] (**15**) as catalyst.

Subsequent studies by Tyler and co-workers also revealed the ability of compounds [$RuCl_2(\eta^6$-arene){$P(NMe_2)_3$}] to promote the hydration of α-hydroxynitriles (cyanohydrins) to the corresponding α-hydroxyamides [74,75], process in which most catalysts fail due to their poisoning by cyanide (generated in aqueous solution by partial decomposition of the cyanohydrins) [76]. Indeed, the well-known Parkins complex

[PtH{($PMe_2O)_2H$}(PMe_2OH)], which has proven to be the most versatile nitrile hydration catalyst reported to date in the literature [77-79], showed only a negligible reactivity against this particular class of substrates [80]. As shown in Scheme 11, complete conversion of glycolonitrile (R = H) and lactonitrile (R = Me) into the corresponding α-hydroxyamides could be achieved at room temperature in the presence of catalytic amounts of [$RuCl_2(\eta^6$-*p*-cymene){$P(NMe_2)_3$}] (**23**) and performing the reactions within the pH range 3.5-8.5 (adjusted by adding HCl or NEt_3 to the aqueous solution) [74,75]. However, we must note that when the ketone-derived cyanohydrin $Me_2C(OH)C{\equiv}N$ and the bulkier mandelonitrile (PhCH(OH)C≡N) were employed as substrates the effectiveness of complex [$RuCl_2(\eta^6$-*p*-cymene){$P(NMe_2)_3$}] (**23**) dropped drastically (up to 22% conversion after 207 h) [75].



Scheme 11. Catalytic hydration of glycolonitrile and lactonitrile using complex [$RuCl_2(\eta^6$-*p*-cymene){$P(NMe_2)_3$}] (**23**).

Concerning their mechanism of action, Tyler and co-workers proposed for this type of catalysts that the tris(dimethylamino)phosphine ligand exerts a cooperative effect during the hydration reactions, activating the water molecule by hydrogen bonding (see Fig. 7). Such a cooperative effect was supported by Density Functional Theory (DFT) calculations employing the hydration of acetonitrile by complex [$RuCl_2(\eta^6$-*p*-cymene){$P(NMe_2)_3$}] (**23**) as model reaction [75].

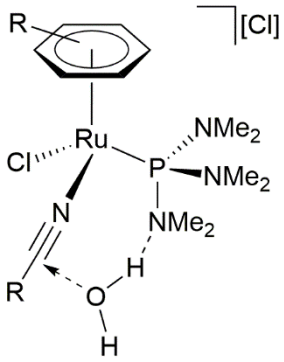
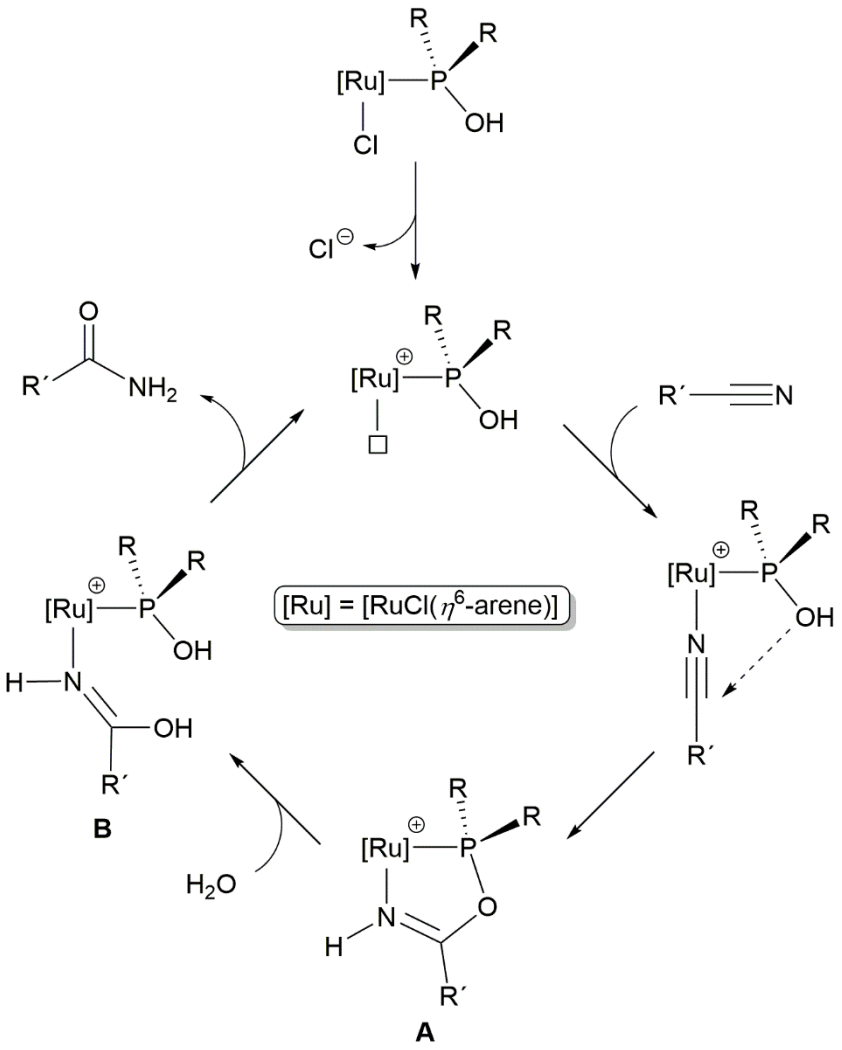


Fig. 7. Proposed cooperative effect of the amino-phosphine ligand $P(NMe_2)_3$.

On the other hand, taking as inspiration Parkin's studies with the hydride-platinum complex $[PtH\{(PMe_2O)_2H\}(PMe_2OH)]$ [77-79], attention has also been paid to the catalytic behaviour of arene-ruthenium(II) complexes with phosphinous acid PR_2OH ligands. In this regard, Tyler and co-workers described the selective hydration of glycolonitrile and lactonitrile employing as catalyst the *p*-cymene derivative $[RuCl_2(\eta^6$-*p*-cymene$)(PMe_2OH)]$ (**24**). Under identical conditions to those indicated in Scheme 11, quantitative transformations were achieved in only 6-17 h, thus improving the previous results with $[RuCl_2(\eta^6$-*p*-cymene$)\{P(NMe_2)_3\}]$ (**23**) [81]. In an independent study, our group compared the activities of compounds $[RuCl_2(\eta^6$-arene$)(PR_2OH)]$ (arene = benzene, *p*-cymene, mesytilene, hmb; R = Me, Ph; all combinations) with those of analogous species with related phosphorous acid-type ligands, *i.e.* compounds $[RuCl_2(\eta^6$-arene$)\{P(OR)_2OH\}]$ (arene = benzene, *p*-cymene, mesytilene, hmb; R = Me, Et, Ph; all combinations), in the hydration of acetonitrile and benzonitrile, with the former leading to faster transformations with both substrates [82]. Among them, complex $[RuCl_2(\eta^6$-*p*-cymene$)(PMe_2OH)]$ (**24**) proved to be the most effective, leading to TOF values of 98 and 1164 h^{-1}, respectively, at 100 ºC [83]. In addition, we also studied theoretically the hydration of acetonitrile by complex $[RuCl_2(\eta^6$-benzene$)(PMe_2OH)]$ through DFT calculations, which confirmed the key participation of the phosphinous acid ligands in these hydration processes [82]. Thus, according to our calculations, the reactions do not proceed through a bifunctional catalysis mechanism in which the OH group of the phosphinous acids assists by H-bonding the nucleophilic attack of the water molecule to the coordinated nitrile as initially assumed by Tyler and co-workers [81]. Instead, a five-membered metallacyclic intermediate **A** is initially generated by intramolecular addition of the OH group of the ligand to the metal-coordinated nitrile, with the subsequent

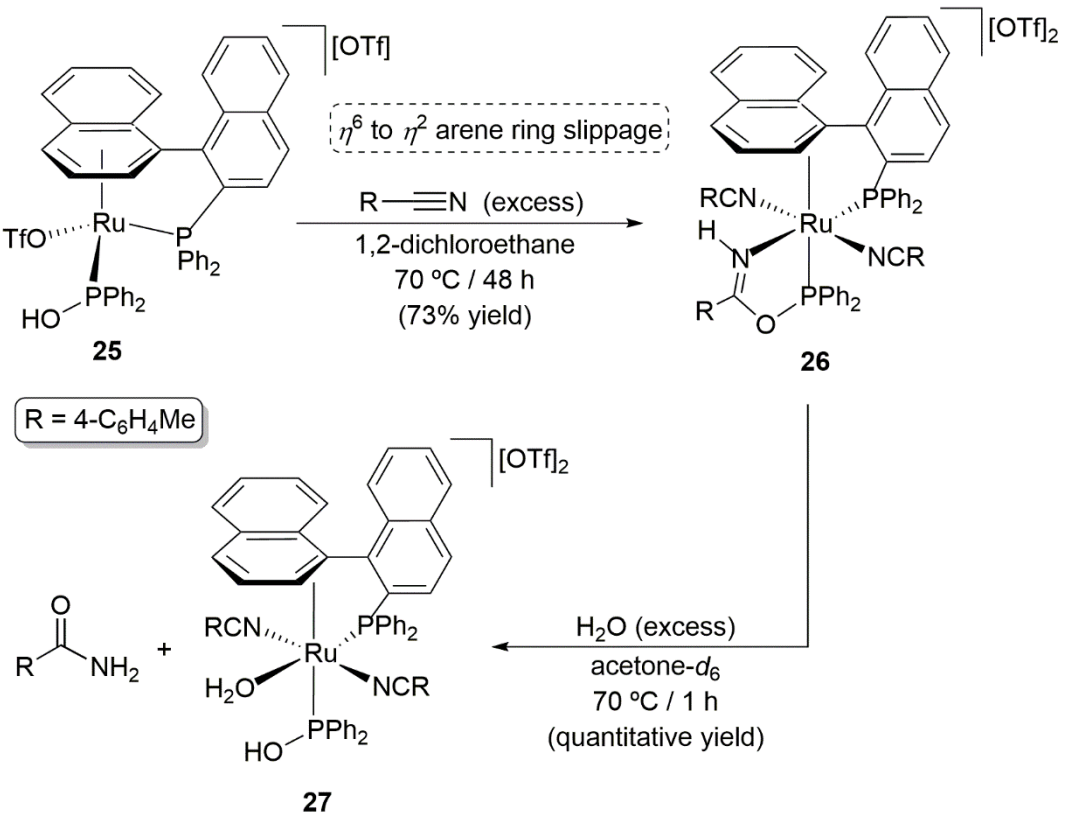
hydrolysis of the metallacycle leading to an iminol complex **B** from which the amide product is liberated after a water-assisted tautomerization (see Scheme 12).



Scheme 12. Mechanism for the hydration of nitriles catalyzed by complexes $[RuCl_2(\eta^6\text{-arene})(PR_2OH)]$.

Although all our attempts to isolate or spectroscopically detect intermediates of type **A** failed, it is important to note that Pregosin and co-workers reported in 2002 the preparation of a related metallacyclic complex **26**, featuring a η^2-coordinated arene, by reacting the "tethered" (η^6-arene)ruthenium(II) derivative **25** with an excess of 4-methylbenzonitrile (Scheme 13) [84]. The structural characterization by single-crystal X-ray diffraction of **26** was subsequently described by us, along with its reactivity towards water. As expected, the reaction of **26** with water leads to the hydrolysis of the ruthenacycle and the formation of the aquo complex **27** and 4-methylbenzamide [85]. In the same work, we also demonstrated the ability of complex **25** to catalyze the hydration

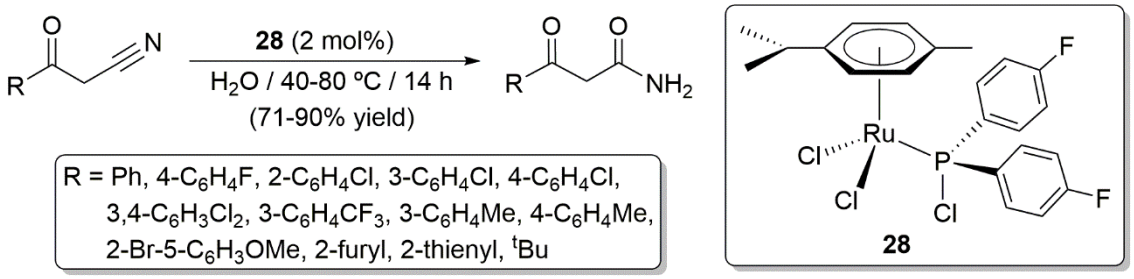
of a diverse family of nitriles in water at 100 ºC (TOF up to 7 h^{-1}), as well as that of the metallacycle **26** to hydrate 4-methylbenzonitrile, experimental results that seem to support the mechanistic proposal depicted in Scheme 12.



Scheme 13. Formation of the metallacyclic complex **26** and its reaction with water.

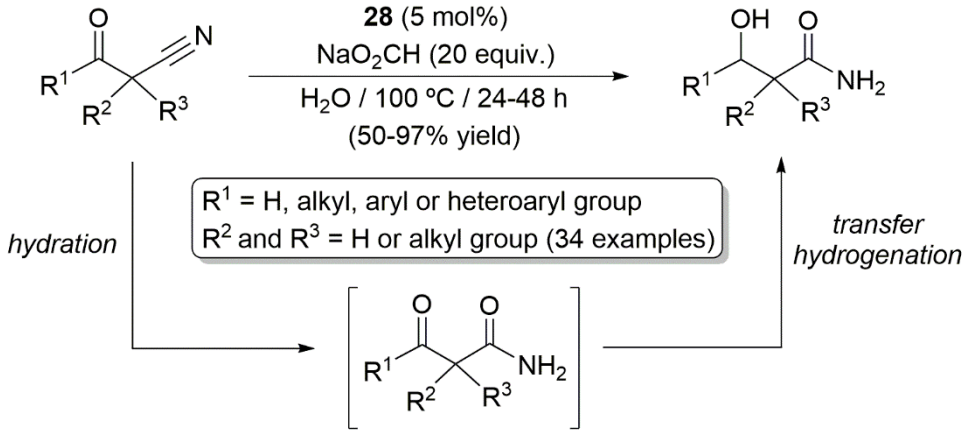
Transition-metal complexes with phosphinous acid-type ligands are usually synthesized by reacting the appropriate metal precursor with a secondary phosphine oxide $R_2P(=O)H$, which in solution tautomerizes into the trivalent form R_2P-OH [86-88]. Alternatively, they can also be accessed by hydrolysis of the phosphorus-halogen bond of coordinated halophosphines [86-88]. This last point opens the possibility of using metal complexes with halophosphines as pre-catalysts in nitrile hydration processes since in the presence of water they would generate the cooperative R_2P-OH ligands. Our group explored this possibility and studied the catalytic behaviour of the *p*-cymene-ruthenium(II) derivatives $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PR_2Cl)]$ (R = Ph, 4-C_6H_4F, 4-$C_6H_4CF_3$, 4-C_6H_4Me, 4-C_6H_4OMe, 2-furyl, Cy, Et), compounds readily accessible by reacting the dimeric precursor $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$ with the corresponding commercially available chlorophosphine [89]. All the complexes proved to be active, with $[RuCl_2(\eta^6\text{-}$

p-cymene){P(4-$C_6H_4F)_2Cl$}] (**28**) showing a remarkable behaviour under mild conditions. Thus, employing 2 mol% of this complex, a large number of aromatic, heteroaromatic, aliphatic and α,β-unsaturated organonitriles could be selectively hydrated at 40 ºC (TOF values up to 100 h^{-1}). Moreover, it was also effective in the hydration of a diverse family of β-ketonitriles, thus allowing the access to synthetically useful β-ketoamides (Scheme 14) [89].



Scheme 14. Catalytic hydration of β-ketonitriles using the arene-Ru(II) complex **28**.

On the other hand, taking advantage of the well-known ability of ruthenium complexes to promote the transfer hydrogenation (TH) of carbonyl compounds by sodium formate in water, we further exploited the synthetic utility of complex [$RuCl_2(\eta^6$-*p*-cymene){P(4-$C_6H_4F)_2Cl$}] (**28**) with the development of an unprecedented and efficient procedure for the direct conversion of β-ketonitriles into β-hydroxyamides involving a tandem hydration/TH process (Scheme 15) [90,91]. An increase in the ruthenium loading (5 mol%) and temperature (100 ºC), along with longer reaction times and the use of an excess of NaO_2CH (20 equiv. with respect to the β-ketonitrile substrate), were required to facilitate the reduction of the corresponding β-ketoamide intermediates, which is the rate-limiting step of the process. The scope of the reaction was very high and could be successfully applied, not only to α-unsubstituted-β-ketonitriles ($R^2 = R^3 = H$), but also to mono- and disubstituted substrates. The only limitation found concerns the use of β-ketonitriles containing aryl substituents on the central α position since the corresponding β-hydroxyamide products were found to be unstable under the basic conditions required for the tandem hydration/TH process to proceed, decomposing through a retro-aldol type reaction [91,92].

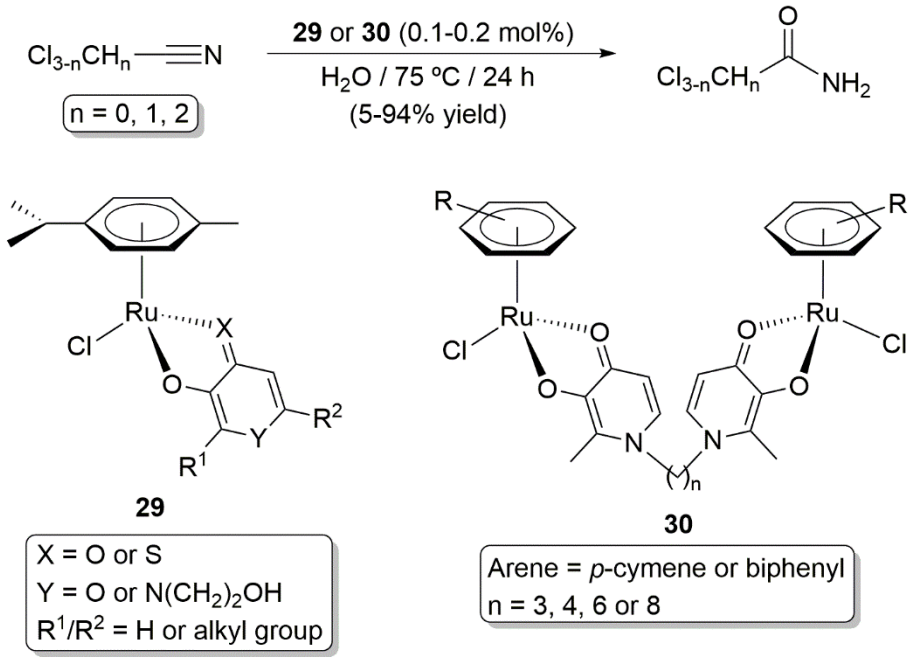


Scheme 15. Direct access to β-hydroxyamides from β-ketonitriles catalysed by the Ru(II) complex **28**.

A very recent study by Vyas and co-workers has revealed the potential of tri(2-furyl)phosphine (PFu_3) as auxiliary *P*-donor ligand for catalytic nitrile hydration reactions [93]. Thus, they found that complex [$RuCl_2(\eta^6$-*p*-cymene)(PFu_3)] (3 mol%) is capable to efficiently hydrate all kind of organonitriles (aromatic, heteroaromatic, aliphatic and α,β-unsaturated) in pure water at 80 ºC and under aerobic conditions (TOF up to 17 h^{-1}), tolerating the presence of common functional groups on the substrates (hydroxyl, nitro, amino, halide, acid, ether, thioether and aldehyde). In addition, the good solubility of [$RuCl_2(\eta^6$-*p*-cymene)(PFu_3)] in water allowed its recycling for four consecutive runs, without substantial loss of activity, by extracting the primary amide product with a suitable organic solvent after each cycle. In the same work, they also evaluated the catalytic behaviour of the cationic species [$RuCl(\eta^6$-*p*-cymene)(PFu_3)$_2$][BF_4] and [$RuCl(\eta^6$-*p*-cymene)(PFu_3)(PTA)][BF_4] which proved to be also active but much less effective since dissociation of the chloride ligand during the reaction to deliver the required vacant site for the coordination of the nitrile is less favoured in these cases.

On the other hand, although to a lesser extent, several phosphine-free arene-ruthenium(II) complexes able to promote C≡N bond hydration reactions can also be found in the literature. In this context, Keppler and co-workers explored in 2008 the hydration of chloroacetonitriles $Cl_{3-n}CH_nC{\equiv}N$ (n = 0, 1, 2) employing different mono- and dinuclear arene-ruthenium(II) complexes **29** and **30**, respectively, containing chelating pyranone-, thiopyranone and pyridinone-based ligands (Scheme 16) [94]. All of them proved to be active in pure water, although not completely selective (selectivity factor ≥ 91%; with formation of the corresponding ammonium chloroacetate as byproduct), generating the

desired chloroacetamides in modest to high yields after 24 h of heating at 75 ºC with metal loadings of 0.1-0.2 mol% (TON and TOF values up to 562 and 39 h^{-1}, respectively).



Scheme 16. Catalytic hydration of chloroacetonitriles by complexes **29** and **30**.

In a more recent study, the group of Jia reported the selective hydration of different benzonitrile derivatives in isopropanol employing as catalysts the *p*-cymene-ruthenium(II) derivatives **31-33**, containing mixed *O*,*N*-donor ligands (see Fig. 8), in combination with NaOH [95]. Among them, the most active one was complex **33**, with which TOF values of up to 92 h^{-1} could be reached at 80 ºC. However, it should be noted that for the hydration process to take place a large amount of base is needed (a stoichiometric amount with respect to the nitrile). In that case, the authors tentatively proposed a hydrido-ruthenium complex as the active species, with the hydride ligand activating the incoming water molecule through a Ru-H···H-OH dihydrogen bonding interaction (see Scheme 17). Such a promoting effect of the hydride ligand had been previously evidenced through DFT calculations by Lau and co-workers in related nitrile hydration reactions promoted by the indenyl-ruthenium(II) derivative [RuH(η^5-C_9H_7)(dppm)] (dppm = bis(diphenylphosphino)methane) [96].

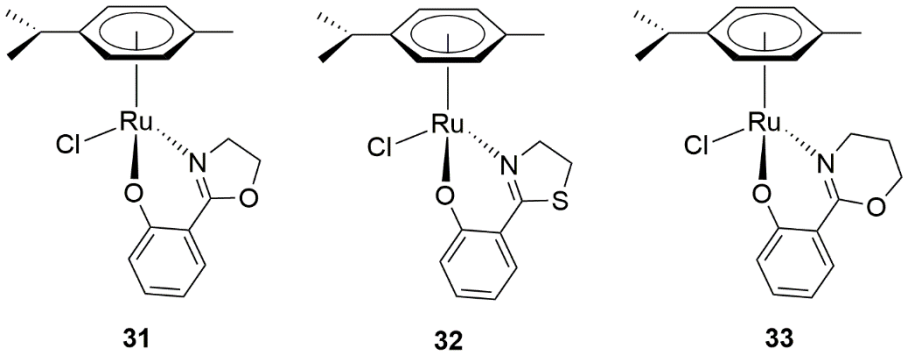
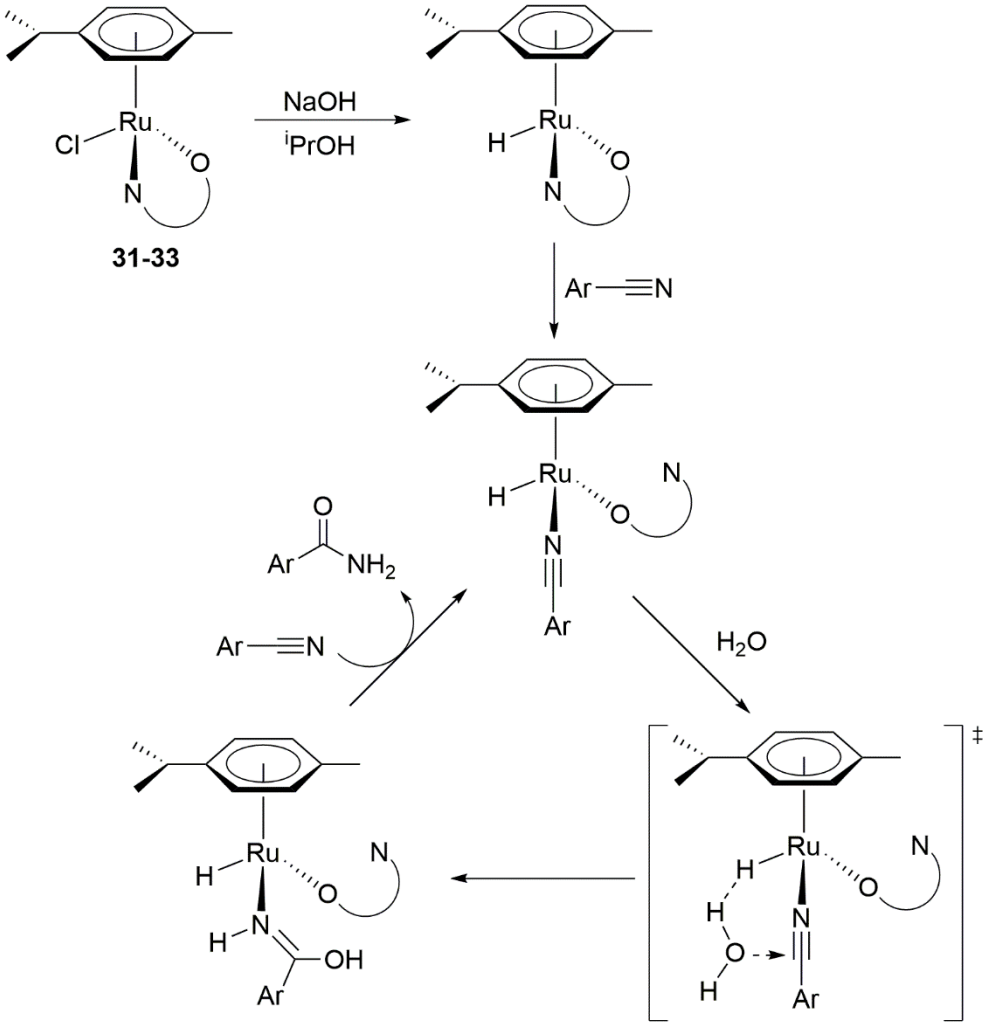


Fig. 8. Structure of the *p*-cymene-ruthenium(II) complexes **31**-**33**.



Scheme 17. Proposed mechanism for the hydration of nitriles catalyzed by complexes **31-33**.

Applying similar reaction conditions, *i.e.* ^{i}PrOH as the solvent, a temperature of 80 ^{o}C and 1 equivalent of base (KOH in this case), the selective conversion of benzonitrile and 4-chlorobenzonitrile into the respective primary amides was also successfully accomplished by Karvembu and co-workers using the *p*-cymene-ruthenium(II) complex

34, which features a bidendate picolyl-based pseudo-acylthiourea ligand (see Fig. 9) [97]. Remarkably, a very low metal loading (0.1 mol%) was required for the reactions to complete, thus allowing to achieve relatively high turnover numbers (TON = 940-970).

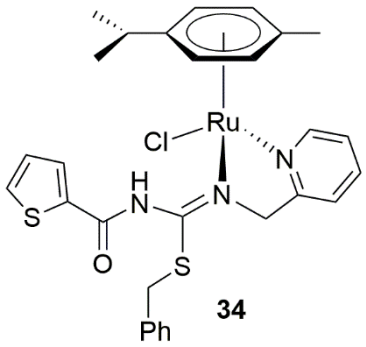
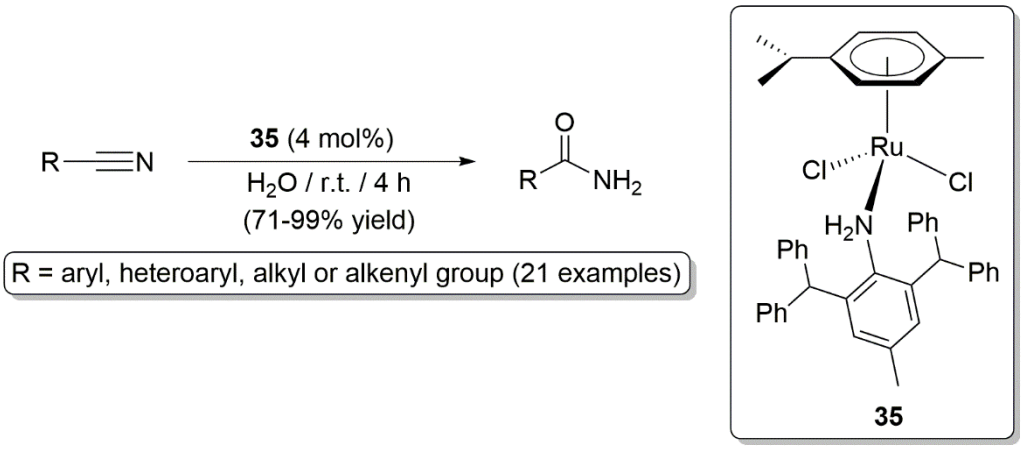


Fig. 9. Structure of the ruthenium(II) complex **34** containing a bidentate pseudo-acylthiourea ligand.

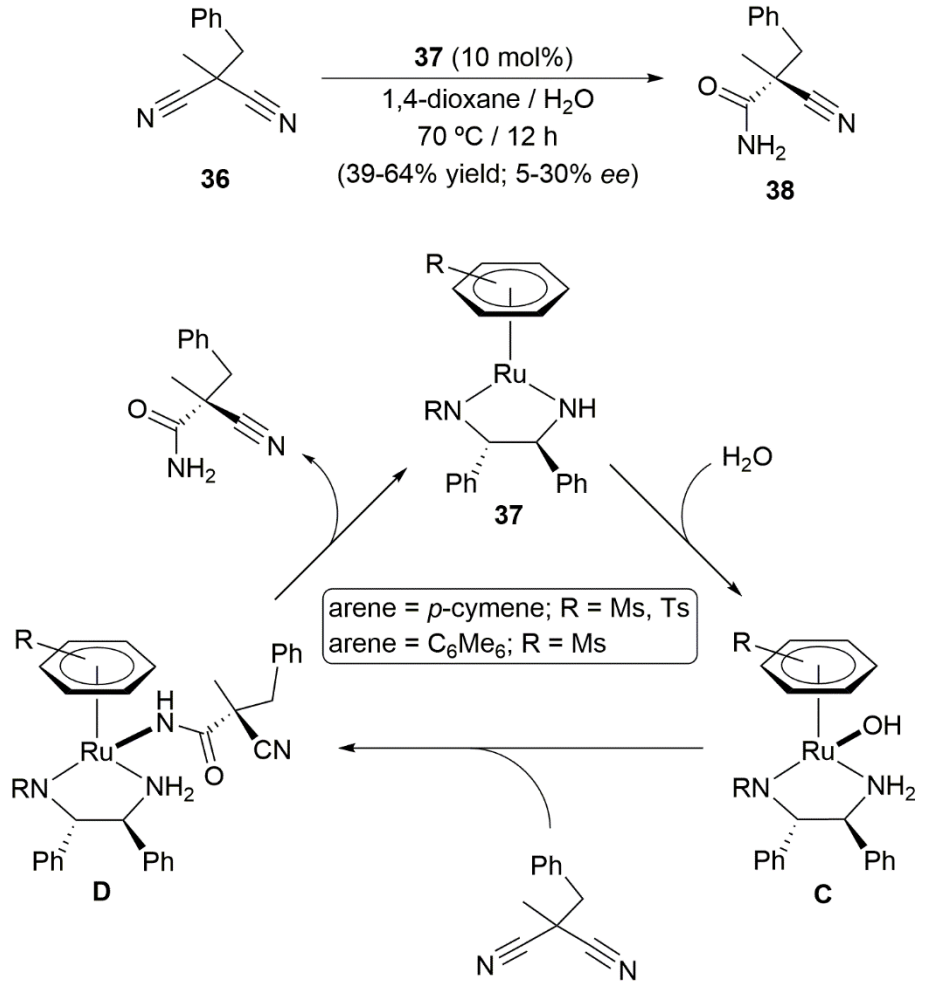
The group of Prabusankar reported in 2018 a more general phosphine-free catalyst, *i.e.* the water-soluble *p*-cymene-ruthenium(II) complex **35** containing as ligand the superbulky amine 2,6-bis(diphenylmethyl)-4-methylaniline, capable to hydrate a variety of aromatic, heteroaromatic, aliphatic and α,β-unsaturated nitriles without the requirement of a base (Scheme 18) [98]. Although the TOF values achieved were relatively low, it must be emphasized the remarkably mild conditions employed (r.t.) and that the use of organic co-solvents was not needed.



Scheme 18. Nitrile hydration reactions catalysed by the superbulky water-soluble complex **35**.

Finally, we must also comment the work by Ikariya and co-workers depicted in Scheme 19. They examined the asymmetric hydration of the prochiral dinitrile α-benzyl-α-methylmalononitrile **36** employing the bifunctional diamido-ruthenium(II) complexes

37 as catalysts. The reactions, which were performed in a mixture 1,4-dioxane/water at 70 ºC, led to the selective formation of the corresponding cyanoamide **38**, albeit in modest yields and with low enantiomeric excesses [99]. According to the authors, the hydration process proceeds through the initial formation of a hydroxo-metal intermediate **C**, *via* deprotonation of one water molecule by the basic diamido ligand. Subsequent reaction of **C** with the dinitrile generates an amidato complex **D**, which finally regenerates **37** by elimination of the cyanoamide product. In favour of this proposal is the fact that both intermediate species **C** and **D** could be isolated through independent experiments carried out under stoichiometric conditions.

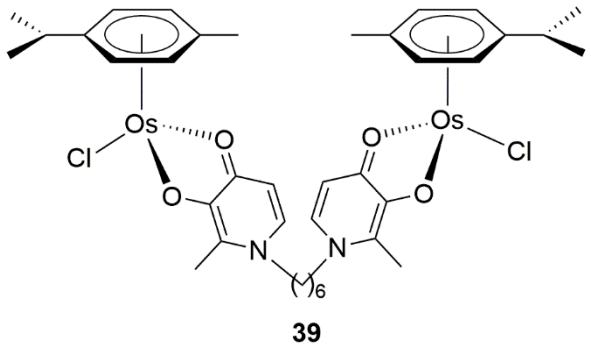


Scheme 19. Asymmetric hydration of the prochiral dinitrile **36**.

2.2. Arene-osmium(II) catalysts

The use of osmium in homogenous catalysis has been for long time underestimated due to its higher cost, and the slower ligand exchange kinetics in its complexes, in comparison to other platinum-group metals [100]. However, several osmium catalysts

featuring outstanding activities in the hydrogenation of ketones [101] and esters [102], the dehydrogenation of alcohols [101] and amines [103], the annulation of functionalized alkynes [104,105], the hydroformylation of olefins [106] or the α-alkylation of ketones and nitriles [107], have been described in recent years, thus demonstrating the enormous potential of this metal in catalytic organic synthesis. In this line, although the application of osmium catalysts in the hydration of nitriles has gone largely unnoticed [108], recent results have shown that arene-osmium(II) complexes can promote these reactions with activities comparable, or even superior, to those of related ruthenium-based systems. This fact was evidenced for the first time in 2008 by Nazarov, Hartinger and co-workers with the dinuclear complex **39** (Fig. 10), which was able to hydrate trichloroacetonitrile into trichloroacetamide with almost the same effectiveness than its ruthenium analog (see Scheme 16) [94].

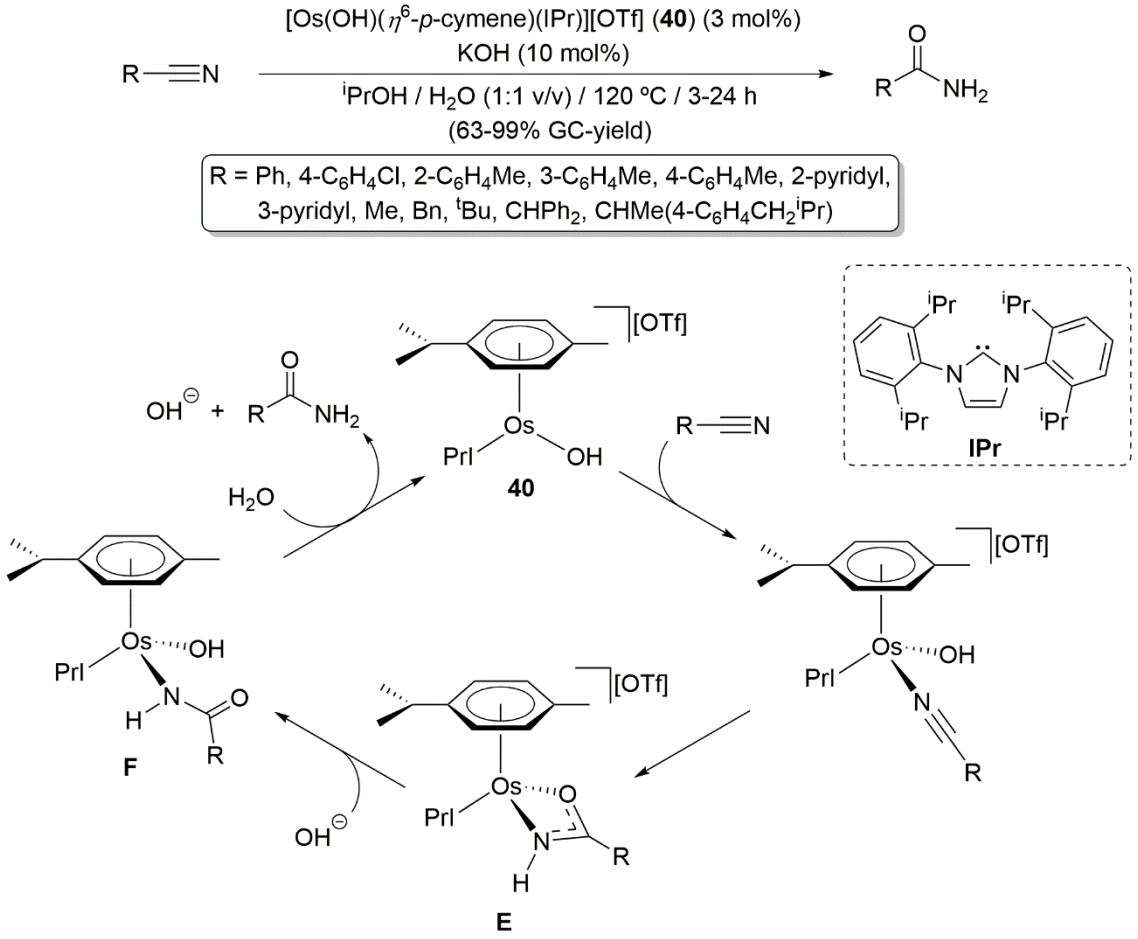


39

Fig. 10. Structure of the dinuclear arene-osmium(II) complex **39**.

A latter study by Esteruelas, Gimeno and co-workers in 2012 revealed the 16-electron hydroxo complex [Os(OH)(η^6-*p*-cymene)(IPr)][OTf] (**40**; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolylidene) as the first general osmium-based catalyst for this transformation [109]. As shown in Scheme 20, in combination with KOH, this complex was able to hydrate in a selective manner a wide range of nitriles at 120 ºC, employing a water/2-propanol mixture as the reaction medium (TON and TOF values up to 33 and 66 h^{-1}, respectively). Concerning the mechanism of the process, DFT calculations as well as experimental observations, indicated that the catalytic reactions proceed through the formation of a cationic κ^2-imidinate intermediate **E**, which is generated by intramolecular addition of the OH ligand to the coordinated nitrile and that can be isolated by performing the reactions under stoichiometric conditions. The subsequent coordination of a hydroxide group (from the KOH present in the medium) to the osmium atom leads to the

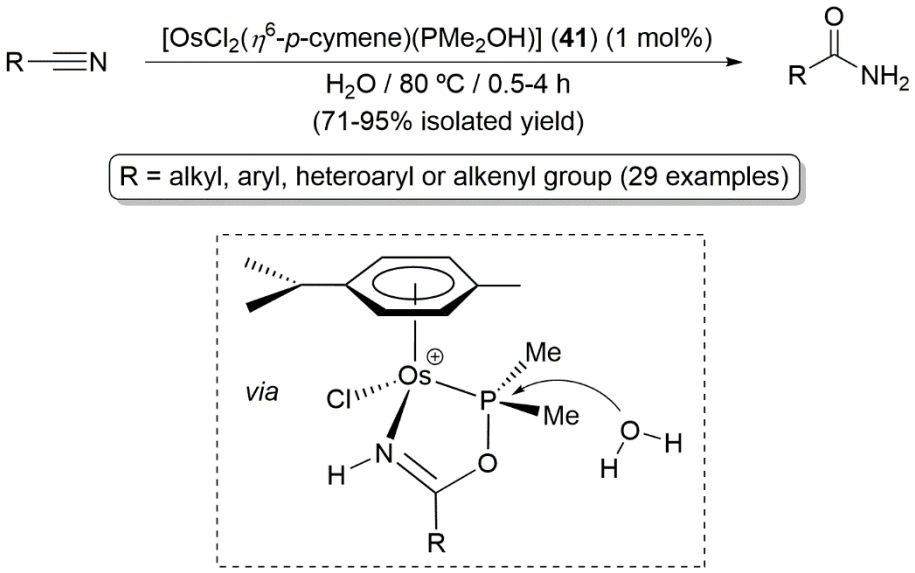
corresponding neutral κ^1-imidinate complex **F**, which by hydrolysis liberates the primary amide product and regenerates the active complex **40**.



Scheme 20. Catalytic hydration of nitriles using [Os(OH)(η^6-*p*-cymene)(IPr)][OTf] (**40**) as catalyst.

Complexes [$OsCl_2$(η^6-*p*-cymene)(PR_2OH)] (R = Me, Ph, OMe, OPh) reported by us are also relevant examples of arene-osmium(II) catalysts for the conversion of nitriles into amides since they can operate in pure water without the assistance of any acidic or basic additive [110]. In terms of activity, the dimethylphosphinous acid derivative [$OsCl_2$(η^6-*p*-cymene)(PMe_2OH)] (**41**) featured the best performances (TOF values up to 200 h^{-1}), and was able to selectively hydrate the C≡N bond of a large variety of aliphatic, aromatic, heteroaromatic and *α,β*-unsaturated nitriles in high yields and short times employing a metal loading of only 1 mol% and a temperature of 80 ºC (Scheme 21). Interestingly, compared to its ruthenium analogue [$RuCl_2$(η^6-*p*-cymene)(PMe_2OH)] (**24**), complex **41** turned out to hydrate faster the usually less reactive aliphatic nitriles, whereas the opposite behaviour was observed for aromatic substrates. These striking trends were

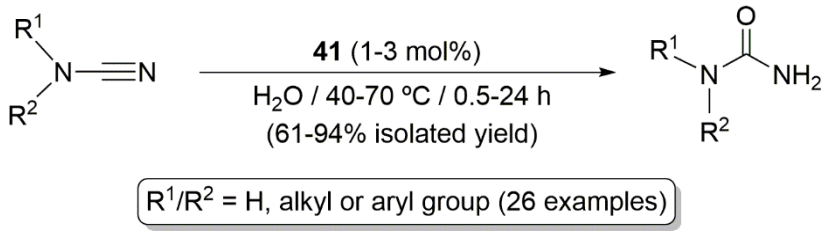
rationalized through DFT calculations. As in the case of ruthenium (see Scheme 12), a reaction pathway involving the generation of a five-membered metallacyclic intermediate, by intramolecular addition of the phosphinous acid ligand to the coordinated nitrile, is also operative with the osmium complex **41**, with subtle differences in the ring strain between the corresponding Os and Ru metallacycles being responsible for the differences in reactivity found.



Scheme 21. Catalytic hydration of nitriles using $[OsCl_2(\eta^6\text{-}p\text{-cymene})(PMe_2OH)]$ (**41**) as catalyst.

We further demonstrated the synthetic utility of complex $[OsCl_2(\eta^6\text{-}p\text{-cymene})(PMe_2OH)]$ (**41**) with the high-yield preparation of a large variety of substituted ureas by hydration of the corresponding cyanamides (Scheme 22), featuring for this particular transformation a superior reactivity to that of $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PMe_2OH)]$ (**24**) [111]. It should be highlighted at this point that compound **41** and **24** represent the first examples of homogeneous catalysts able to hydrate cyanamides reported to date in the literature, process in which the Parkins catalyst $[PtH\{(PMe_2O)_2H\}(PMe_2OH)]$ is completely inoperative [111]. The reactions, which tolerated the presence of several functional groups, proceeded with exquisite selectivity at 40-70 ºC, employing water as the sole solvent, in the absence of additives, and with low metal loadings (1-3 mol%). In addition, under these remarkably mild conditions, the reaction rates observed were faster than those involving classical aliphatic and aromatic nitriles. Computational calculations indicated that the higher reaction rates observed with the cyanamide substrates are associated with the inductive effect exerted by the N atom, which reduces the electron

density on the nitrilic carbon, thus favouring the intramolecular nucleophilic attack of the OH group of the phosphinous acid ligand to this carbon.



Scheme 22. Catalytic hydration of cyanamides using [$OsCl_2(\eta^6$-*p*-cymene)(PMe_2OH)] (**41**) as catalyst.

The (η^6-*p*-cymene)-osmium(II) derivatives **42-44a,b**, containing mono-, bis- and trisamino phosphine ligands (Fig. 11), reported by our group proved to be also catalytically active in the hydration of organonitriles [112]. As in the precedent case, they are able to operate in pure water without the requirement of any acidic or basic additive, with [$OsCl_2(\eta^6$-*p*-cymene){$PPh_2(NMe_2)$}] (**42a**) being the most effective. Thus, using 1 mol% of this complex and performing the catalytic reactions at 100 ºC, a large variety of aliphatic, aromatic, heteroaromatic and *α,β*-unsaturated nitriles (26 examples) could be selectively converted into the corresponding primary amides in high yields and short times (TOF up to 200 h^{-1}). Remarkably, under identical experimental conditions, the activity of [$OsCl_2(\eta^6$-*p*-cymene){$PPh_2(NMe_2)$}] (**42a**) was found to be superior to that of other transition metal complexes containing the same amino-phosphine ligand, such as [$RuCl_2(\eta^6$-*p*-cymene){$PPh_2(NMe_2)$}], [$RuCl_2(\eta^3$:η^3-$C_{10}H_{16}$){$PPh_2(NMe_2)$}], *cis*-[$PtCl_2${$PPh_2(NMe_2)$}$_2$] or [RhCl(cod){$PPh_2(NMe_2)$}] (cod = 1,5-cyclooctadiene), as well as that of the triphenylphosphine derivative [$OsCl_2(\eta^6$-*p*-cymene)(PPh_3)], thus pointing out the enormous potential of osmium and the beneficial effect exerted by the amino-phosphines in this catalytic transformation. With regard to this last point, NMR studies with aqueous solutions of **42a** indicated that, upon heating, hydrolysis of the P-N bond of the $PPh_2(NMe_2)$ ligand readily takes place leading to the formation of the phosphinous acid derivative [$OsCl_2(\eta^6$-*p*-cymene)(PPh_2OH)], which probably acts as the real catalyst. As commented previously, a cooperative action of the amino-phosphine ligands *via* H-bonding with the water molecules had been proposed by Tyler and co-workers for related ruthenium-based catalysts. However, the observations made with [$OsCl_2(\eta^6$-*p*-cymene){$PPh_2(NMe_2)$}] (**42a**) suggest that the role played by the amino-phosphine

ligands in these previous studies should be reconsidered (precursors of phosphinous acids instead of simple H-bond acceptors).

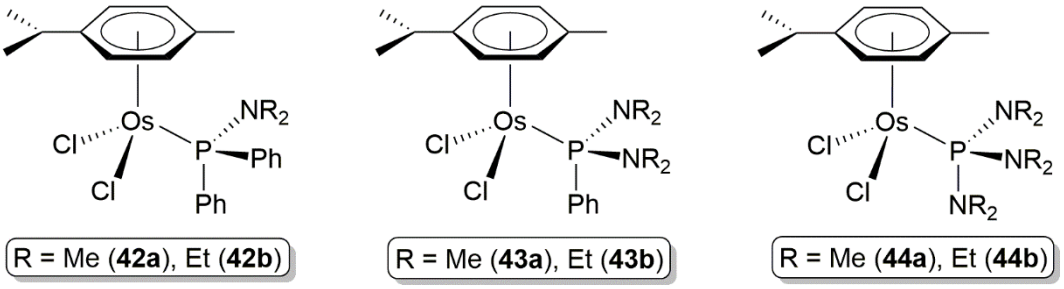
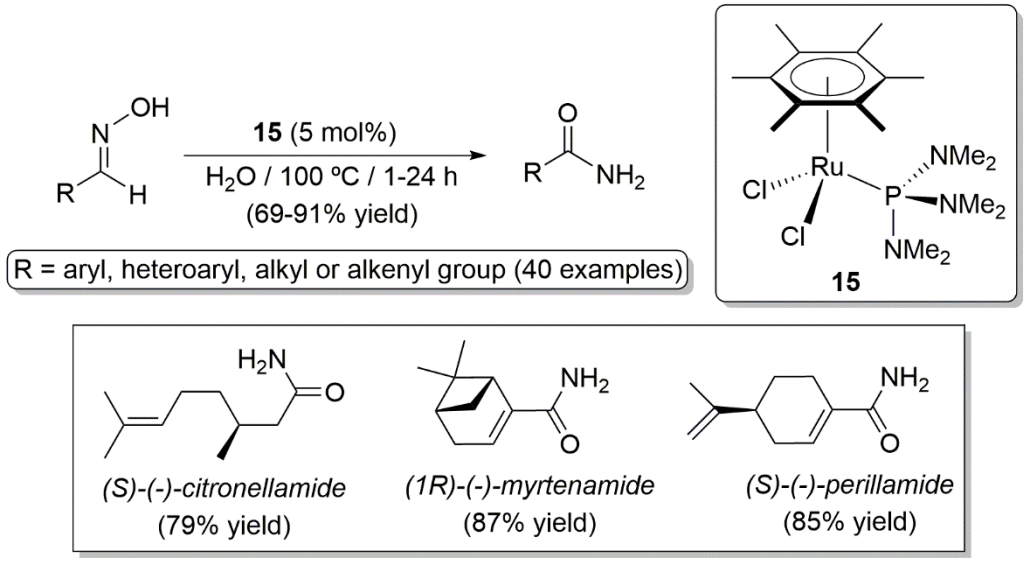


Fig. 11. Structure of the amino-phosphine cymene-osmium(II) complexes **42-44a,b**.

3. Aldoximes rearrangement reactions

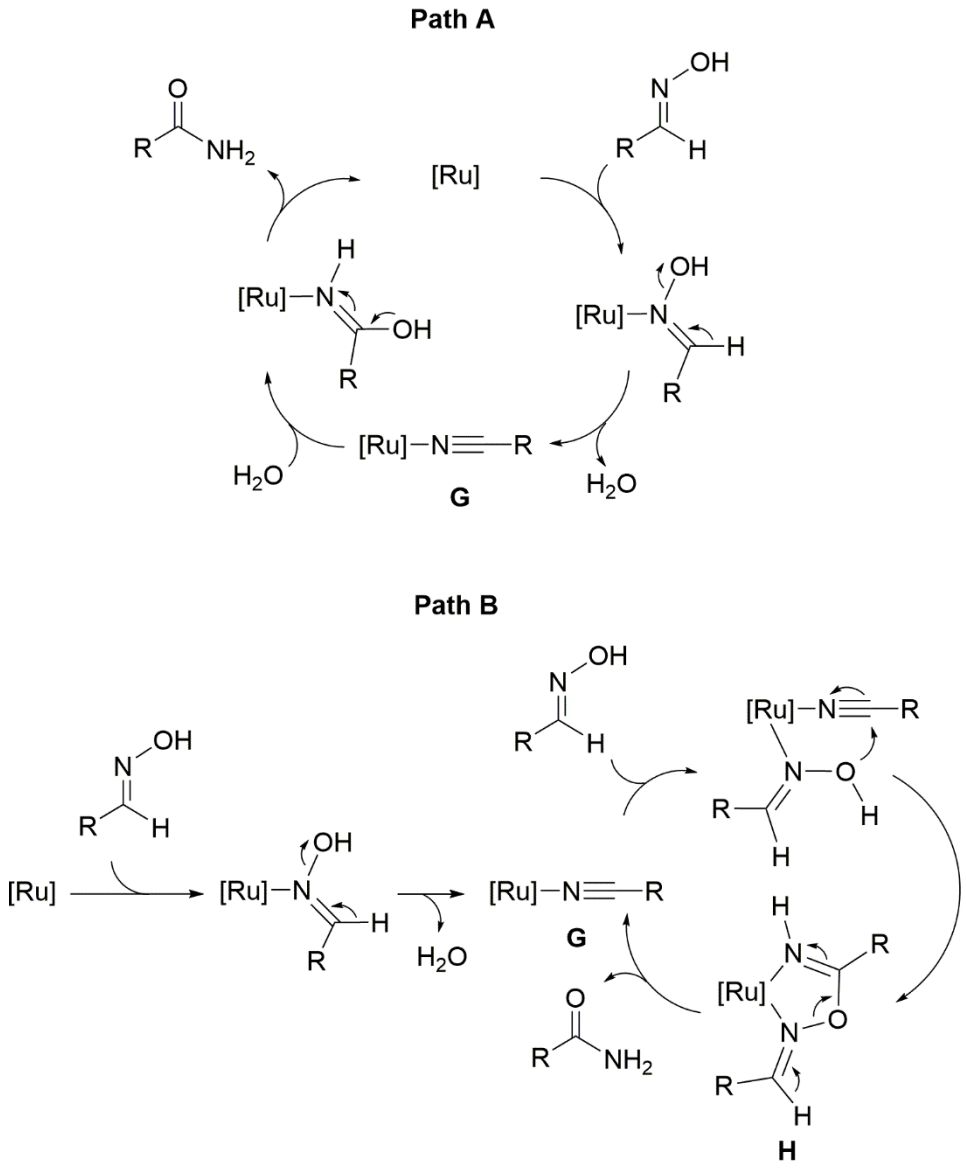
3.1. Arene-ruthenium(II) catalysts

Among the different transition metal complexes able to catalyze the rearrangement of aldoximes to amides, those based on ruthenium have been probably the most widely studied [42,45-47]. In this context, taking advantage of the excellent performances shown by the water-soluble tris(dimethylamino)phosphine-ruthenium(II) complex [$RuCl_2(\eta^6$-hmb){$P(NMe_2)_3$}] (**15**) in the hydration of nitriles, our group developed the first protocol for the selective conversion of aldoximes to primary amides in water under homogeneous conditions [113]. The reactions proceeded cleanly at 100 ºC using 5 mol% of this complex, did not required of any additive, and were compatible with the presence of common functional groups in the substrates, such as hydroxyl, nitro, ethers, thioethers, halides or amino (Scheme 23). In addition, the synthetic utility of the process was demonstrated with high yield preparation of the chiral amides (*S*)-(-)-citronellamide, (*S*)-(-)-perillamide and (1*R*)-(-)-myrtenamide, compounds of interest in the fragrances field (see Scheme 23).



Scheme 23. Catalytic rearrangement of aldoximes in water using complex **15** as catalyst.

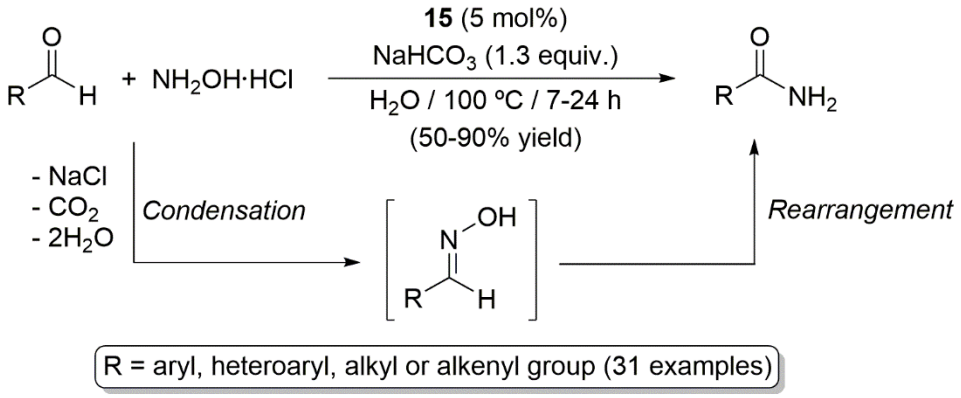
Kinetic studies and experiments performed in ^{18}O-labeled water indicated that the rearrangement reactions depicted in Scheme 23 proceed simultaneously through two different mechanisms (paths A and B in Scheme 24). In the first one (path A), the aldoxime is initially dehydrated into the corresponding nitrile upon coordination to the ruthenium center (intermediate **G**), and the nitrile subsequently hydrated by the water molecule released in the previous step. The second one (path B) also starts with the dehydration of the aldoxime into a nitrile, which is now hydrated by a second molecule of aldoxime *via* the metallacyclic intermediate **H**. Of these two reaction pathways, the second one is the predominant and explains the low ^{18}O-incorporation (*ca.* 15%) in the amide product observed when the rearrangement of the model benzaldoxime was carried out employing ^{18}O-labeled water as the solvent.



Scheme 24. Reaction pathways for the aldoxime-to-amide rearrangements promoted by complex **15**.

As shown in Scheme 25, complex [$RuCl_2(\eta^6$-hmb){$P(NMe_2)_3$}] (**15**) proved to be also a suitable catalyst for the rearrangement of aldoximes generated *in situ* from the corresponding aldehydes [114]. The reactions proceeded again in refluxing water, just by adding to the medium 1.3 equivalents of hydroxylamine hydrochloride and a base ($NaHCO_3$) to neutralize the HCl liberated during the initial condensation step. This *one-pot* procedure for the preparation of primary amides from aldehydes resulted to be applicable to a huge number of aromatic, heteroaromatic, aliphatic and *α,β*-unsaturated substrates, and allowed for example the high yield preparation of ferrocenecarboxamide, a valuable starting material in the chemistry of ferrocene, starting from commercially available ferrocenecarboxaldehyde. It is also important to note that some of these

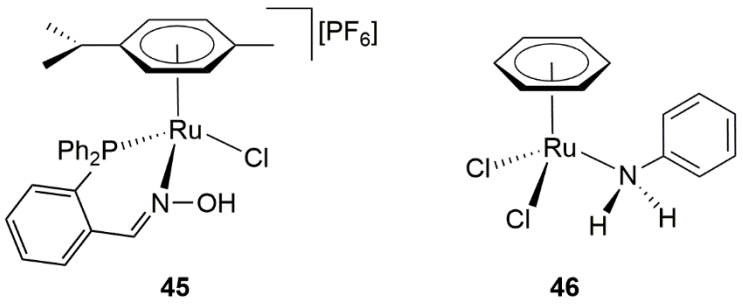
amidation reactions were equally effective employing a commercially available hydroxylamine solution (50 wt% in H_2O), instead of the $NH_2OH{\cdot}HCl/NaHCO_3$ combination, thus allowing to improve notably the atom economy of the overall process since water is the only by-product formed in this case [114].



Scheme 25. One-pot synthesis of primary amides from aldehydes in water using complex **15** as catalyst.

In a later study we also demonstrated the utility of *p*-cymene-ruthenium complex **14**, containing a tri-cationic thiazolyl-phosphine hydrochloride salt as ligand (see Scheme 8), for the synthesis of different aromatic and aliphatic primary amides in water starting from aldoximes or the respective aldehydes [70]. This catalyst showed an effectiveness superior to that of **15** for both processes, allowing to obtain the amides in high yields (≥ 78%) with a ruthenium loading of only 3 mol% (reactions performed at 100 ºC for 7 h; starting from aldehydes 1.3 equiv. of $NH_2OH{\cdot}HCl$ and $NaHCO_3$ were employed). Further examples of arene-ruthenium(II) catalysts able to promote aldoxime-to-amide rearrangements in aqueous medium reported by us are the "tethered" derivative **25** (see Scheme 13) [85] and the cationic complex $[RuCl(\eta^6\text{-}p\text{-cymene})\{\kappa^2\text{-}(P,N)\text{-}2\text{-}Ph_2PC_6H_4CH{=}NOH\}][PF_6]$ (**45** in Fig. 12) [115]. The performances of both compounds were comparable to that of $[RuCl_2(\eta^6\text{-hmb})\{P(NMe_2)_3\}]$ (**15**), although it should be noted that in the case of **45** a co-catalyst, *i.e.* the halide abstractor $AgSF_6$, was needed to facilitate the generation of a vacant site on the metal. On the other hand, a work published by Singh's group in 2015 also brought out the usefulness of the phosphine-free complex $[RuCl_2(\eta^6\text{-benzene})(NH_2Ph)]$ (**46** in Fig. 12) as catalyst for the *one-pot* conversion of aldehydes to primary amides in water [116]. The scope and functional group tolerance of **46**, which is capable of promoting the process at 60 ºC, was very high (26 examples with yields in the range 45-99% after 5-24 h, employing a 5 mol% of **46** and 1.3 equiv. of

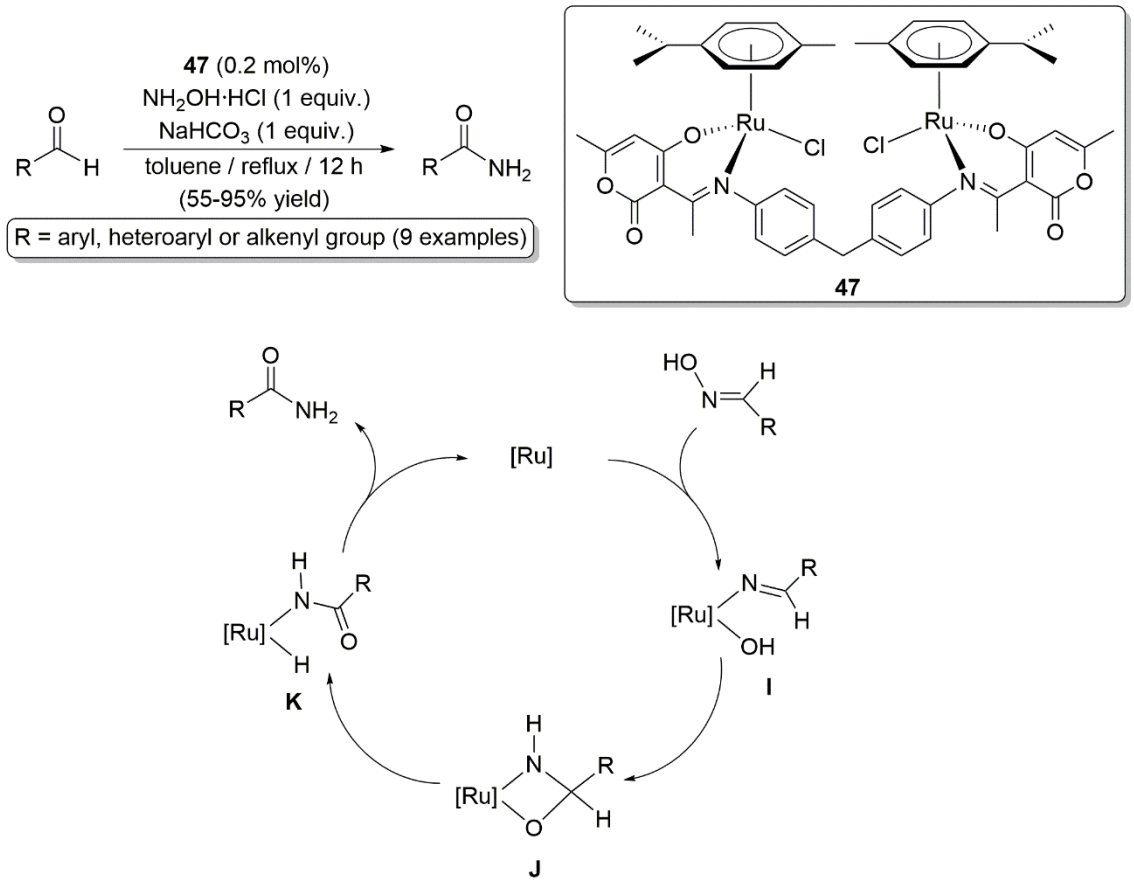
$NH_2OH{\cdot}HCl$ and $NaHCO_3$). According to the authors, the aldoxime rearrangement step proceeds through a mechanism similar to that of path B depicted in Scheme 24.



45 **46**

Fig. 12. Structure of the arene-ruthenium(II) complexes **45** and **46**.

Catalytic systems for the *one-pot* conversion of aldehydes to primary amides in organic media based on arene-ruthenium(II) complexes have also been described in the literature. In this context, Raja and Therrien reported this type of reactions in refluxing toluene using catalytic amounts of the dinuclear derivative **47**, hydroxylamine hydrochloride as the "NH_2 source" and $NaHCO_3$ as the base [117]. As shown in Scheme 26, different aromatic, heteroaromatic and α,β-unsaturated primary amides could be obtained in moderate to high yields after 12 h of heating with a catalyst loading of only 0.2 mol%. For the aldoxime rearrangement step, the authors proposed in this case the involvement of a hydroxo-metal complex **I**, generated by oxidative addition of the aldoxime to one of the ruthenium centers (Scheme 26). Once formed, this intermediate would evolve into the κ^1-imidinate complex **J** by intramolecular addition of the OH ligand to the N=CHR one, which subsequently undergoes a β-hydride elimination to form **K**. In the final step of the catalytic cycle the primary amide product is liberated by reductive elimination.



Scheme 26. Catalytic synthesis of primary amides from aldehydes catalysed by the dinuclear complex **47**.

On the other hand, the groups of Joshi and Venkatachalam evaluated the catalytic potential of the mononuclear complexes depicted in Fig. 13, containing chelating pyrazolated chalcogenoethers, *i.e.* compounds **48** [118], and phenolate-azo mixed *O*,*N*-donor ligands, *i.e.* compounds **49**, respectively [119]. Both showed to be effective for the conversion of different aromatic and heteroaromatic aldehydes into the corresponding primary amides in refluxing toluene or acetonitrile, employing hydroxylamine hydrochloride in combination with a base ($NaHCO_3$ or NaOH) and low ruthenium loadings (0.1-1 mol%). In the case of compounds **48**, the involvement of an hydroxo-ruthenium intermediate was again proposed for the rearrangement of the *in situ* formed aldoxime, although its generation and the role it plays in the catalytic cycle differ substantially from the ones discussed above (see Scheme 27).

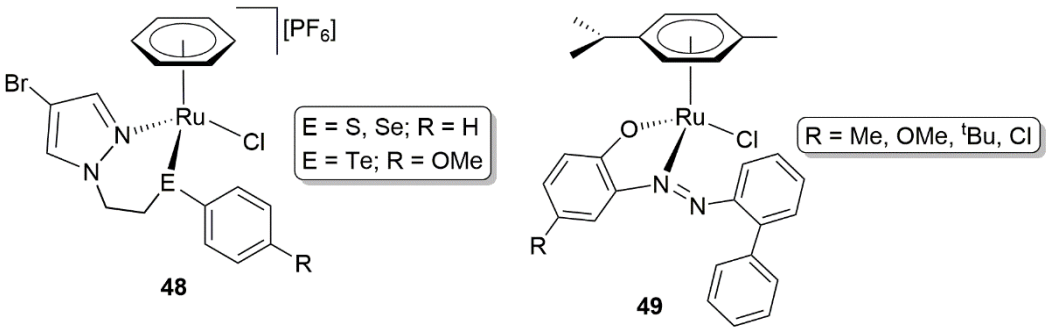
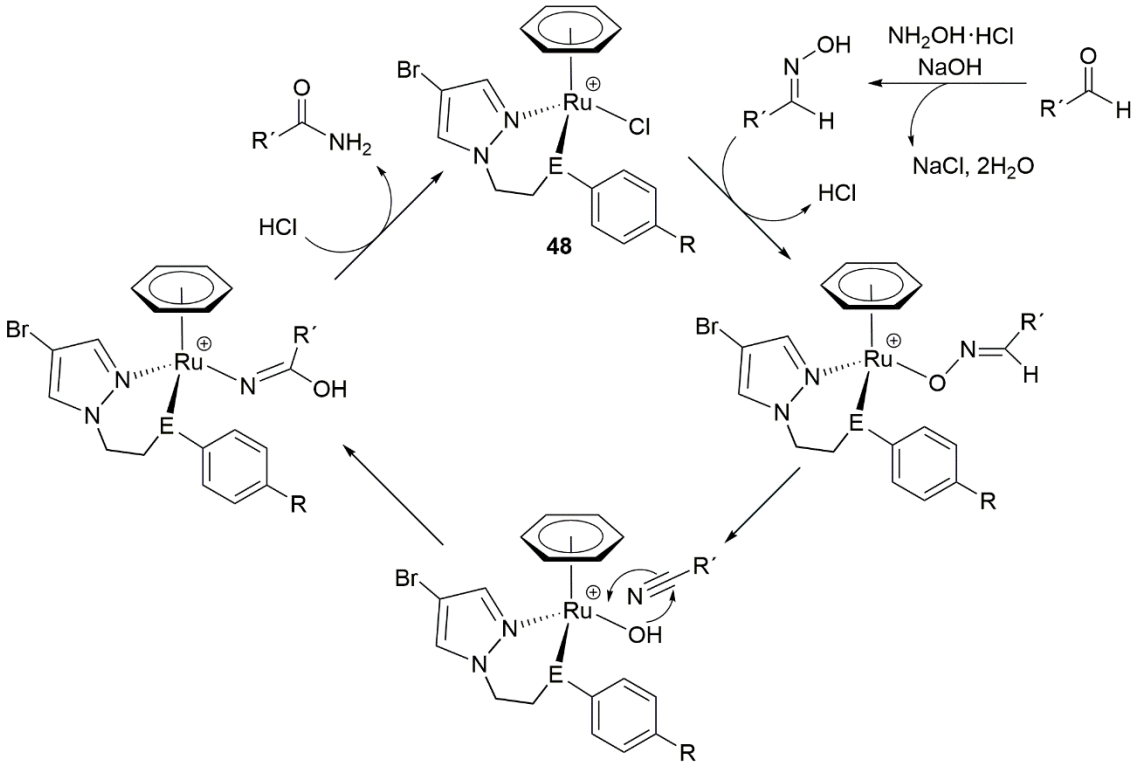


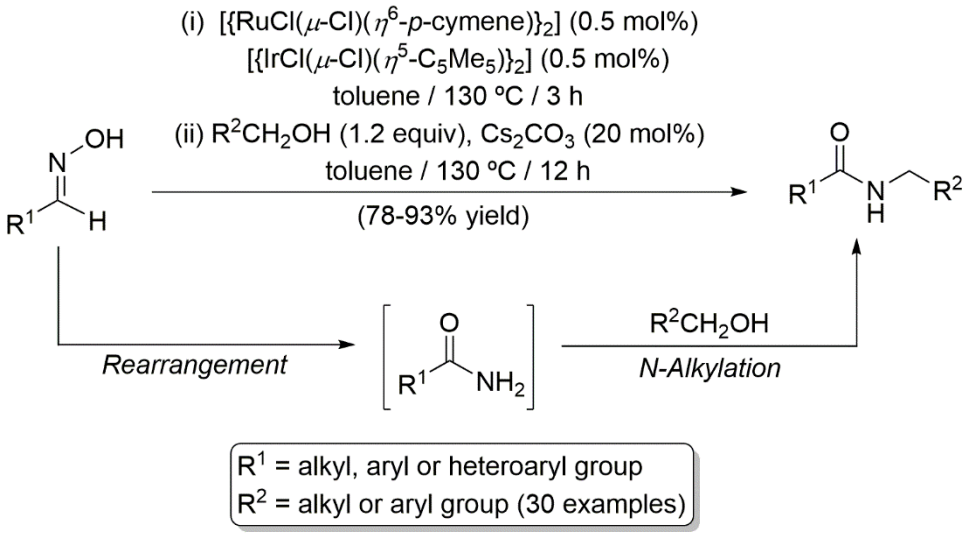
Fig. 13. Structure of the mononuclear arene-ruthenium(II) complexes **48** and **49**.



Scheme 27. Mechanism proposed for catalytic reactions promoted by complexes **48**.

Finally, we must mention that, using a catalytic system composed of the Ru(II) and Ir(III) dimers [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] and [{IrCl(μ-Cl)(η^5-C_5Me_5)}$_2$], Li and co-workers were able to develop an efficient procedure for the *one-pot* synthesis of secondary amides from aldoximes and primary alcohols through a sequential rearrangement/*N*-alkylation process (Scheme 28) [120]. The reactions were carried out by heating at 130 ºC a toluene solution of the aldoxime and the catalysts for 3 h, and subsequent addition of the alcohol and a base (Cs_2CO_3) to the medium with further heating for additional 12 h. Although the two steps involved in the process, *i.e*. the rearrangement of the aldoxime into the corresponding primary amide and the *N*-alkylation

of the latter, can be promoted by both catalysts alone, the combination of the two metals resulted more advantageous than their use separately since [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] proved more effective than [{IrCl(μ-Cl)(η^5-C_5Me_5)}$_2$] in the first step and the opposite in the second. The scope of the process was very high and a variety of aromatic, heteroaromatic and aliphatic aldoximes, as well as different benzylic and aliphatic alcohols, could be satisfactorily employed.



Scheme 28. Catalytic synthesis of secondary amides from aldoximes and primary alcohols.

3.2. Arene-osmium(II) catalysts

To the best of our knowledge, catalytic systems for the rearrangement of aldoximes to amides based on osmium complexes have not been yet appeared in the literature. However, it should be mentioned that, when exploring the catalytic potential of the arene-osmium(II)-guanidinate complexes **50** (see Fig. 14) in dehydration reactions of aldoximes to generate nitriles, our group systematically observed the presence of minor amounts of the corresponding primary amides in the reaction crudes [121]. This observation leaves open the possibility of developing effective osmium catalysts for this particular transformation in the near future.

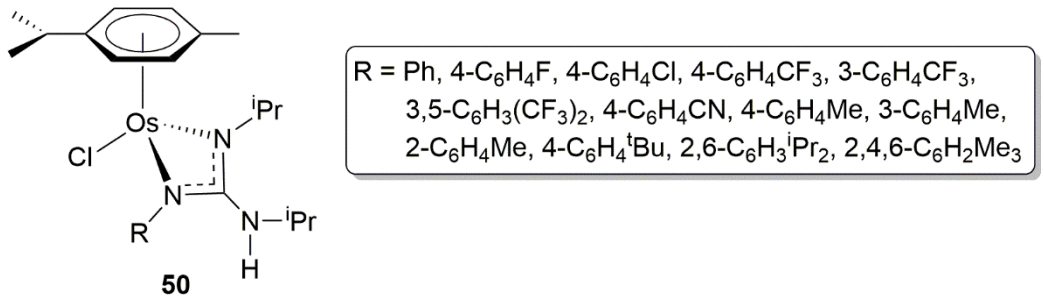


Fig. 14. Structure of the half-sandwich guanidinate-osmium(II) complexes **50**.

4. Conclusions

In this review article we have presented a comprehensive account of the application of arene-ruthenium(II) and osmium(II) complexes as catalysts in primary amides formation reactions through nitrile hydration and aldoxime rearrangement processes. As the reader will have noticed, this type of compounds represents an excellent platform for the screening of ligands with potential cooperative properties. In fact, some of the systems developed to date have shown activities and selectivities far superior to those achieved with other transition metal catalysts, allowing in most cases to carry out these transformations under mild conditions, in the absence of additives and/or employing environmentally friendly water as solvent. Obviously, the field remain open with many opportunities for new discoveries, particularly with regard of osmium-based catalysts, and we hope that this article will inspire future works in this direction.

5. Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

6. Acknowledgments

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FOR GRAPHICAL ABSTRACT USE ONLY

Arene-ruthenium(II) and osmium(II) complexes as catalysts for nitrile hydration and aldoxime rearrangement reactions

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Given their ease of access, modularity and robustness, arene-ruthenium(II) complexes have been extensively employed as catalysts for the formation of primary amides through nitrile hydration and aldoxime rearrangement reactions. Very recently, some arene-osmium(II) derivatives has also demonstrated their effectiveness in the catalytic hydration of nitriles. A survey of this chemistry is herein presented.