EurJIC
European Journal of Inorganic Chemistry

Minireviews
doi.org/10.1002/ejic.202100413

Chemistry Europe
European Chemical Societies Publishing

Access to α- and β-Hydroxyamides and Ureas Through Metal-Catalyzed C≡N Bond Hydration and Transfer Hydration Reactions

Pascale Crochet[a] and Victorio Cadierno*[a]

Dedicated to Prof. Christian Bruneau for his outstanding contributions in homogeneous catalysis.

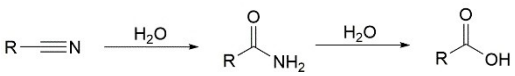
The hydration of nitriles is an important transformation because the resulting primary amides present a huge number of applications in synthetic organic chemistry, as well as industrial and pharmaceutical interest. Metallic compounds (complexes, oxides, and nanoparticles) are known to catalyze the hydration of nitriles by activating the nitrile substrate, the water molecule, or both partners, upon coordination. In this Minireview article, the application of metal-based catalysts in the hydration of α- and β-hydroxynitriles and cyanamides is comprehensively discussed. Compared to more classical organonitriles, little attention has been paid to the hydration of these particular class of substrates despite the synthetic relevance of the respective carboxamides, *i.e.* α-/β-hydroxyamides and ureas. Transfer hydration strategies, in which a water surrogate is employed to convert the C≡N group into the C(=O)NH_2 one, are also covered.

1. Introduction

Amides are versatile synthetic intermediates and building blocks present in biomolecules, such as proteins, and commonly found in natural products, pharmaceuticals, pesticides, and functional materials.[1] In keeping with their wide applications, chemical reactions for the formation of amide bonds are among the most executed transformations in organic chemistry. In this regard, the most classical strategies for amide synthesis involve the reaction of amines with activated carboxylic acid derivatives.[1,2] However, these processes feature a low atom economy as they usually require the use of stoichiometric amounts of coupling reagents, with the search for greener alternatives being identified by the ACS GCIPR (American Chemical Society Green Chemistry Institute® Pharmaceutical Roundtable) as a priority area of research for the pharmaceutical industry.[3] In the continuous search for improved synthetic methods, metal-catalyzed transformations have emerged in the last two decades as the most promising alternatives for the atom-economical and cost-effective access to amides, offering the possibility of using a large variety of staring materials in addition to the carboxylic acids and their derivatives.[4] In this context, the metal-catalyzed hydration of nitriles represents nowadays one of the most convenient methods to obtain primary amides, offering several advantages over the conventional acid- and base-promoted transformations such as milder reaction conditions, broader tolerance to functional groups, and higher chemoselectivity (*i.e.* the desired amides are not further hydrolyzed to the corresponding carboxylic acids; see Scheme 1).[5] In addition, compared to enzymatic procedures, metal-based catalysts are easier to handle, generally cheaper, and provide a wider substrate scope.[6]

Countless homogenous and heterogeneous catalysts capable to selectively convert nitriles to primary amides have been described to data, with those based on ruthenium, rhodium, nickel, palladium, platinum and gold being by far the most studied.[5] From a mechanistic point of view, although different reaction pathways have been proposed for these metal-catalyzed transformations, activation of the nitrile by coordination to the metal center is a common prerequisite for all of them. In this way, the C≡N unit becomes more electrophilic and susceptible to the nucleophilic attack by the water molecule (or a hydroxyl group if basic conditions are employed). The addition process can occur both in an inter- or intramolecular manner, with a hydroxo-complex being generally postulated as intermediate in the second case (see Scheme 2).[5]

Regarding homogeneous catalysts design, the most innovative aspects in the field have focused on the development of bifunctional systems, in which functionalized auxiliary ligands present in the coordination sphere of the metal facilitate the addition of the water molecule to the coordinated nitrile by



Scheme 1. Nitrile hydration and amide hydrolysis reactions.

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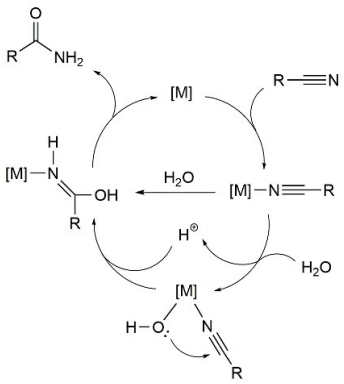


Scheme 2. Commonly proposed reaction pathways in metal-catalyzed nitrile hydration reactions.

activation of the former through a secondary hydrogen-bond interaction (Figure 1).[5]

On the other hand, several catalytic protocols for the selective conversion of nitriles to primary amides under anhydrous conditions have also been disclosed in recent years, employing aldoximes or amides as water surrogates (see Scheme 3).[7] In these transfer hydration processes, an H_2O molecule is formally transferred from the water donor to the nitrile substrate, thus leading to the desired amide product with concomitant release of the corresponding nitrile fragment $R^2C{\equiv}N$. Aldoximes and amides leading to volatile nitriles $R^2C{\equiv}N$, such as acetaldoxime, propionaldoxime or acetamide, are usually employed in order to facilitate the isolation of the primary amides. Compared to classical metal-catalyzed nitrile hydration reactions, the mechanistic information on these transfer hydration processes is much scarcer. However, in the case of aldoximes, it is commonly proposed that the H_2O-transfer occurs upon activation of the nitrile substrate by the metal (**A**). In this way, a metal-iminol intermediate **B** is generated, from which the amide product is released. Regarding the use of amides as the water source, free or metal-

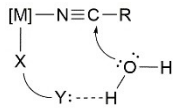
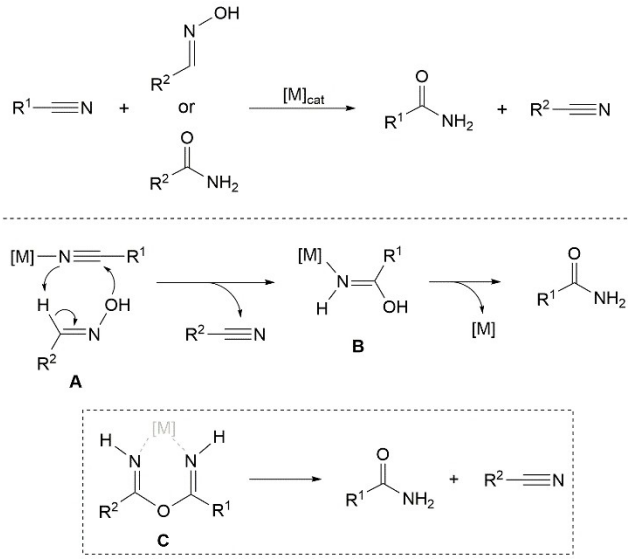


Figure 1. Simplified representation of the cooperative ligand effect in metal-catalyzed nitrile hydration reactions.



Scheme 3. Hydration of nitriles using aldoximes or primary amides as water surrogates.

coordinated imidic anhydride intermediates of type **C**, resulting from the hydroamidation of the nitrile, have been postulated.[7]

The aim of the present Minireview article is to provide a comprehensive overview of the application of these metal-catalyzed hydration and transfer hydration processes in the preparation of α-hydroamides (**D**), β-hydroxyamides (**E**) and ureas (**F**) (see Figure 2) from the corresponding organonitriles. We must emphasize at this point that, despite the synthetic relevance of compounds **D**–**F**, catalytic systems capable to

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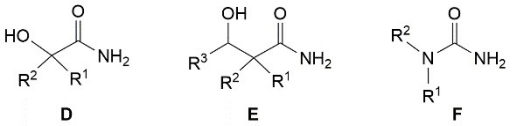


Figure 2. Structure of the carboxamide-containing compounds **D**–**F**.

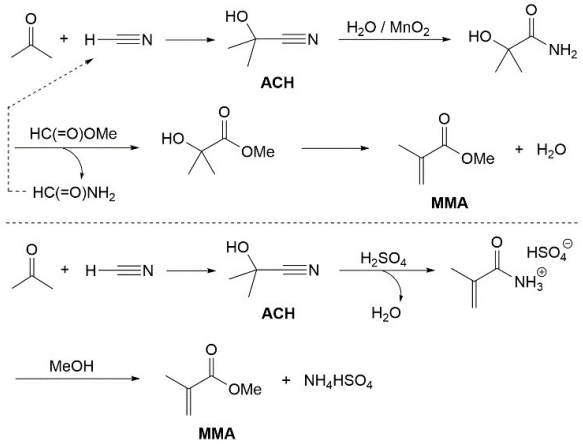
hydrate α/β-hydroxynitriles and cyanamides are yet relatively scarce and most of them have only seen the light very recently.

2. α-Hydroxyamides

α-Hydroxyamides are structural motifs present in a huge number of biologically active molecules,[8] and valuable building blocks in synthetic organic chemistry.[9] Hence, several methods for the preparation of this type of compounds have been developed, with the chemoselective reduction of α-ketoamides being probably the most popular approach.[10] Ideally, hydration of α-hydroxynitriles (also referred to as cyanohydrins), readily available by cyanation of aldehydes or ketones, would represent the simplest option to access *N*-unsubstituted α-hydroxyamides, but limited success has been achieved to data in the hydration of this particular class of nitriles.[5c] The main problem lies in the intrinsic instability of the cyanohydrins, which tends to decompose in solution into the corresponding carbonyl compounds and hydrogen cyanide (HCN), a process particularly favored at high temperatures or under basic conditions (Scheme 4).

Nonetheless, it should be noted at this point that hydration of some aldehyde-derived cyanohydrins, the more stable ones, has been successfully achieved employing borate salts as catalysts.[11] Hydration of more challenging ketone-derived cyanohydrins using MnO_2-based catalysts has also been documented in several patents.[12] Indeed, based on the MnO_2-catalyzed hydration of acetone cyanohydrin (ACH), the Mitsubishi Gas Chemical company, developed in 1997 a new process for the production of the methyl methacrylate (MMA) monomer (Scheme 5; top). It involves initial ACH synthesis from acetone and HCN, selective hydration of ACH to generate 2-hydroxyisobutylamide, subsequent esterification with methylformate, and final dehydration into MMA. Compared to the previous industrial procedure for the MMA production from ACH, the use of sulphuric acid to hydrate ACH is avoided and, consequently, the generation of large amounts of ammonium bisulfate waste after the final esterification step (Scheme 5; bottom).[13]

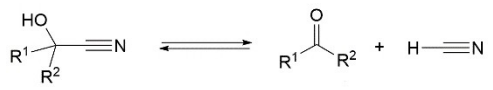
The fact that cyanohydrins slowly decompose in solution releasing HCN makes the vast majority of metal catalysts for the



Scheme 5. Schematic MMA production routes from ACH.

hydration of organonitriles inoperative with this particular class of substrates, since the irreversible coordination of the cyanide anion to the metal deactivates them. This cyanide poisoning was first revealed by Tyler's group in 2009 when trying to hydrate different cyanohydrins with the Parkins platinum catalyst [PtH{$(PMe_2O)_2H$}(PMe_2OH)] (**1**; see Figure 3),[14] which has proven to be the most versatile and effective catalyst in nitrile hydration reported to date in the literature.[15,16] Indeed, complex **1** was capable to hydrate only the aliphatic aldehyde-derived cyanohydrins lactonitrile and 2-hydroxybutyronitrile, *i.e.* RCH(OH)C≡N (R = Me, Et), in moderate yield (up 68%) after several days, resulting inoperative when faced to glycolonitrile (CH_2(OH)C≡N), mandelonitrile (PhCH(OH)C≡N), acetone cyanohydrin and cyclohexanone cyanohydrin.[14]

A few years later, Tyler and co-workers were able to improve these results by using the half-sandwich Ru(II) complex [$RuCl_2(\eta^6$-*p*-cymene){$P(NMe_2)_3$}] (**2**) as catalyst (Scheme 6).[17] Complex **2** incorporates the cooperative $P(NMe_2)_3$ ligand, which is known to accelerate nitrile hydration reactions by activating the nucleophilic water molecule by hydrogen bonding (intermediate **G**).[18] In particular, they achieved the quantitative hydration of glycolonitrile, in water at room temperature, with 5 mol% of **2** after 42 h.[19] Full conversion of lactonitrile into 2-hydroxypropanamide was also possible, although the required reaction time was longer and the hydration process had to be carried out at an acidic pH (adjusted by adding HCl to the medium). In general, the cyanohydrin decomposition equilibrium favors cyanohydrins at low pH; hence why the reaction was run at pH 3.5. In the case of the parent glycolonitrile, an acidic medium was not necessary given its greater stability.



Scheme 4. The decomposition equilibrium of cyanohydrins.

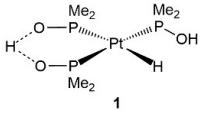
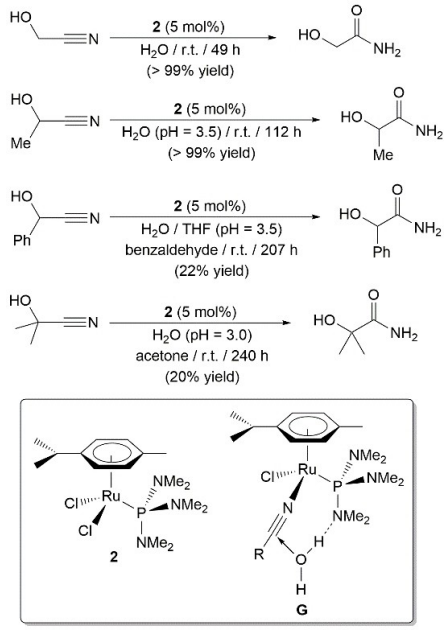
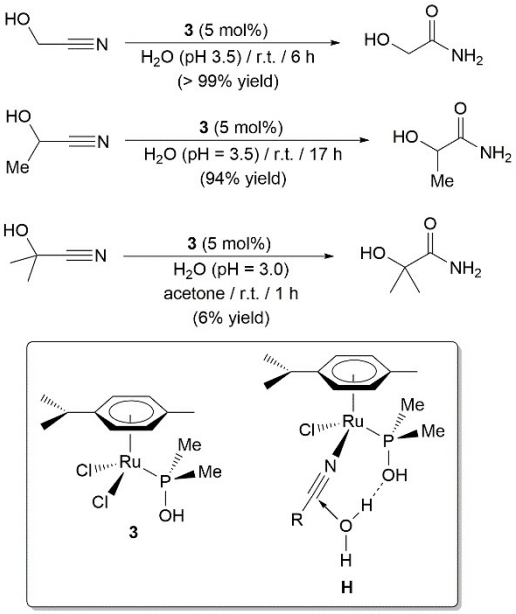


Figure 3. Structure of the Parkins nitrile hydration catalyst **1**.



Scheme 6. Hydration of cyanohydrins catalyzed by the Ru(II) complex **2**.

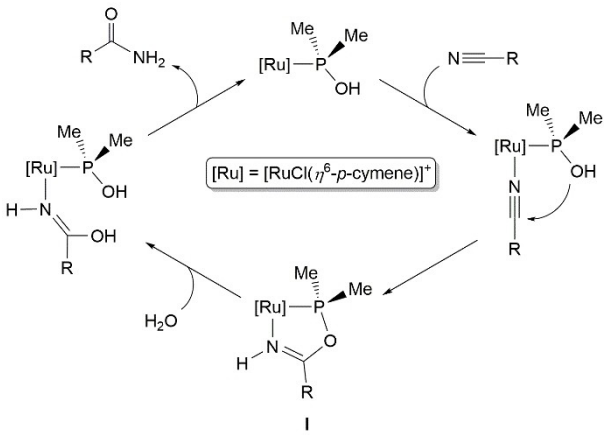


Scheme 7. Hydration of cyanohydrins catalyzed by the phosphinous acid-based ruthenium(II) complex **3**.

Although in low yield (20–22%), more challenging substrates, such as mandelonitrile or acetone cyanohydrin, were also hydrated by complex [$RuCl_2(\eta^6$-*p*-cymene){$P(NMe_2)_3$}] (**2**) performing the reactions at pH 3.0–3.5 (see Scheme 6). In these cases, benzaldehyde and acetone were additionally added to the reaction medium to further minimize the decomposition of the substrates.

Performing the reactions at acidic pH, hydration of glycolonitrile and lactonitrile was also successfully accomplished by the same group using the phosphinous acid-based ruthenium (II) complex [$RuCl_2(\eta^6$-*p*-cymene)(PMe_2OH)] (**3**) (Scheme 7).[20] In comparison with [$RuCl_2(\eta^6$-*p*-cymene){$P(NMe_2)_3$}] (**2**), faster transformations were observed. This fact is in complete accord with the greater effectiveness shown by complex **3** in the hydration of classical organonitriles.[20,21] Hydration of acetone cyanohydrin using [$RuCl_2(\eta^6$-*p*-cymene)(PMe_2OH)] (**3**) was also attempted, but no more than 6% conversion was reached, a result that points to a higher sensitivity of complex **3** *vs* **2** to cyanide (see Scheme 7).[20]

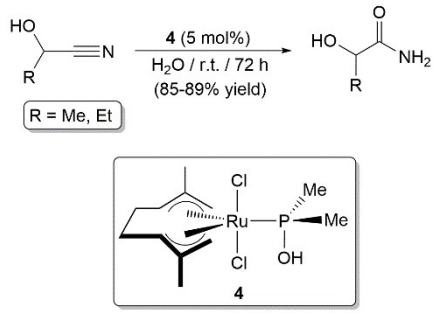
Regarding the mechanism of action of complex [$RuCl_2(\eta^6$-*p*-cymene)(PMe_2OH)] (**3**), Tyler and co-workers assumed that, as in the case of **2**, it favors the hydration reactions by H-bond activation of the incoming water molecule with the OH substituent of the *P*-donor ligand (intermediate **H** in Scheme 7).[20] However, we must note that this assumption is wrong since a subsequent theoretical analysis of the hydration mechanism carried out by our group revealed a different role of the dimethylphosphinous acid ligand Me_2POH.[21] Thus, the Density Functional Theory (DFT) calculations indicated that the phosphinous acid ligand participates in the hydration process through the formation of a five-membered metallacyclic intermediate **I** by addition of the OH group to the coordinated nitrile (Scheme 8). This metallacycle is subsequently opened,



Scheme 8. Catalytic cycle for the nitrile hydration reactions catalyzed by complex [$RuCl_2(\eta^6$-*p*-cymene)(PMe_2OH)] (**3**).

through the attack of a water molecule on the phosphorus atom, releasing the amide product and regenerating the catalytically active species.

Further studies by our group showed that the related phosphinous acid-based ruthenium(IV) complex [$RuCl_2(\eta^3{:}\eta^3$–$C_{10}H_{16}$)(PMe_2OH)] (**4**; $C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl) is also effective in hydrating lactonitrile and 2-hydroxybutyronitrile.[22] As shown in Scheme 9, performing the reactions in pure water, the corresponding α-hydroxyamides were generated in high yield (85–89%) without the need to control the pH of the medium. However, we must note that attempts to hydrate aromatic cyanohydrins, such as mandelonitrile, employing the same reaction conditions were unsuccessful. Poisoning of the catalyst by cyanide was observed due the



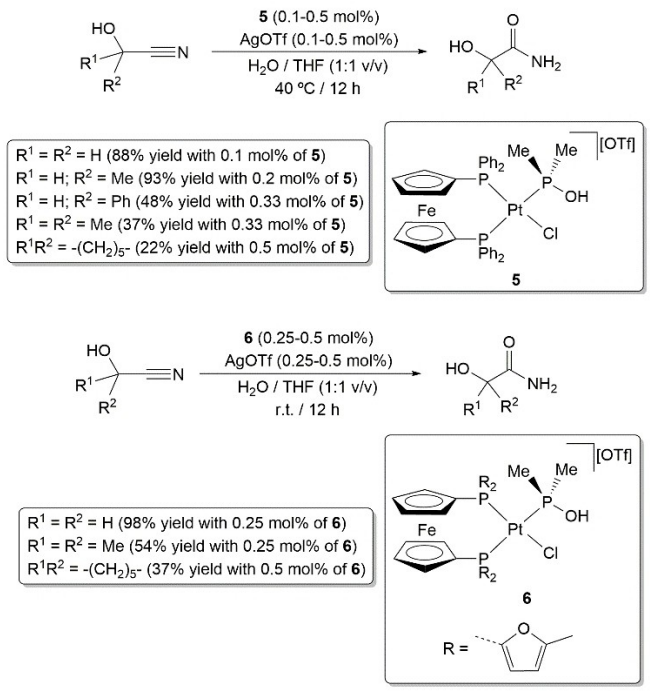
Scheme 9. Hydration of lactonitrile and 2-hydroxybutyronitrile catalyzed by the phosphinous acid-based bis(allyl)-ruthenium(IV) complex **4**.

faster decomposition of the mandelonitrile derivatives compared to their aliphatic counterparts.

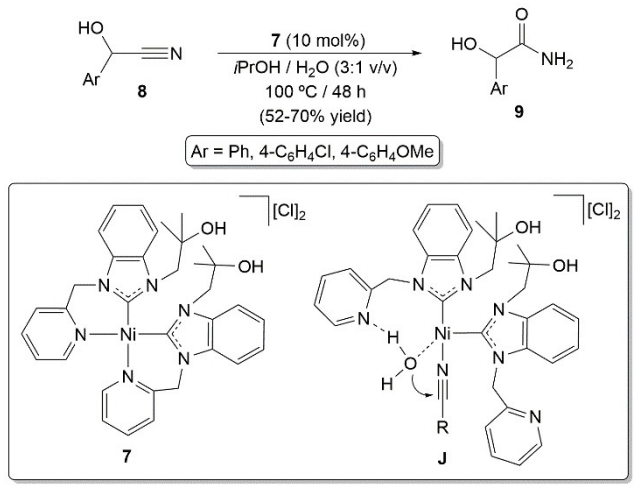
The utility of Me_2POH as auxiliary ligand in the design of transition metal catalysts capable to hydrate cyanohydrins was further evidenced by Virgil, Grubbs and co-workers with the cationic platinum(II) complex [PtCl(ddpf)(PMe_2OH)][OTf] (**5**; dppf = 1,1'-bis(diphenylphosphino)ferrocene).[23] As shown in Scheme 10, in conjunction with silver(I) triflate, this complex was able to hydrate under neutral conditions glycolonitrile, lactonitrile, mandelonitrile, acetone cyanohydrin and cyclohexanone cyanohydrin, in THF/H_2O mixtures at 40 °C, employing remarkably low metal loadings (0.1–0.5 mol%). Once again, the different stability of the substrates was reflected in the yields with which the corresponding α-hydroxyamide products were obtained. In particular, starting from acetone cyanohydrin and cyclohexanone cyanohydrin the amide yield was only 37% and 22%, respectively, values that could be increased to 54% and 37% employing the modified catalyst **6** containing the more electron-rich 1,1'-bis[bis(5-methyl-2-furanyl)phosphino] ferrocene ligand instead of the dppf one. The higher activity of complex **6** allowed also to run the reactions at room temperature (see Scheme 10).

On the other hand, Bera and co-workers reported in 2017 the catalytic hydration of a broad range of nitriles under neutral conditions employing the dicationic Ni(II) complex **7**, featuring two chelated pyridyl- and hydroxyl-functionalized *N*-heterocyclic carbene (NHC) ligands, as catalyst.[24] Complex **7** showed a remarkable activity as a consequence of the hemilabile behavior and H-bonding properties of the pendant pyridyl wingtips, which allow the simultaneous activation of both the nitrile and water molecules (intermediate **J** in Scheme 11). Mandelonitriles **8** were part of the substrates tested in the study. Although they could be converted in moderate yield into the corresponding α-hydroxyamides **9** by performing the reactions in a *i*PrOH/water mixture at 100 °C for 48 h with 10 mol% of complex **7**, the conditions employed were more demanding than those required by classical organonitriles (70 °C, 2 mol% of **7** and reaction times of 6–24 h), illustrating again the challenge associated with these functionalized nitriles.

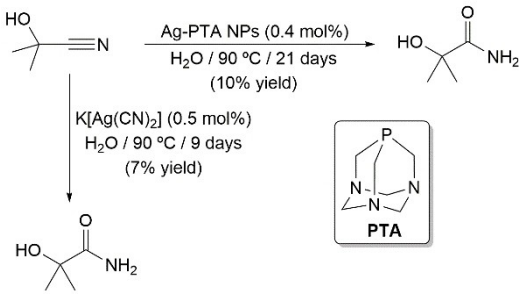
In addition to the homogeneous catalysts just commented, the behavior of metal nanoparticles (NPs) in the hydration of cyanohydrins has also been documented. In particular, the group of Tyler synthesized water-soluble Ag NPs, stabilized by the hydrophilic 1,3,5-triaza-7-phosphaadamantane ligand (PTA), which proved to be active in the hydration of acetone cyanohydrin in water at 90 °C (Scheme 12).[25] Although a maximum amide yield of 10% was achieved before the complete decomposition of the substrate into acetone and HCN, the solution remained active upon addition of a second, and even a third, aliquot of acetone cyanohydrin, thus pointing out that the catalytically active species are not poisoned by the cyanide present in the medium. In this respect, further experiments suggested that the silver(I) cyanide complex $[Ag(CN)_2]^-$,



Scheme 10. Hydration of cyanohydrins catalyzed by the cationic phosphinous acid-based platinum(II) complexes **5** and **6**.



Scheme 11. Nickel-catalyzed hydration of madelonitriles **8**.



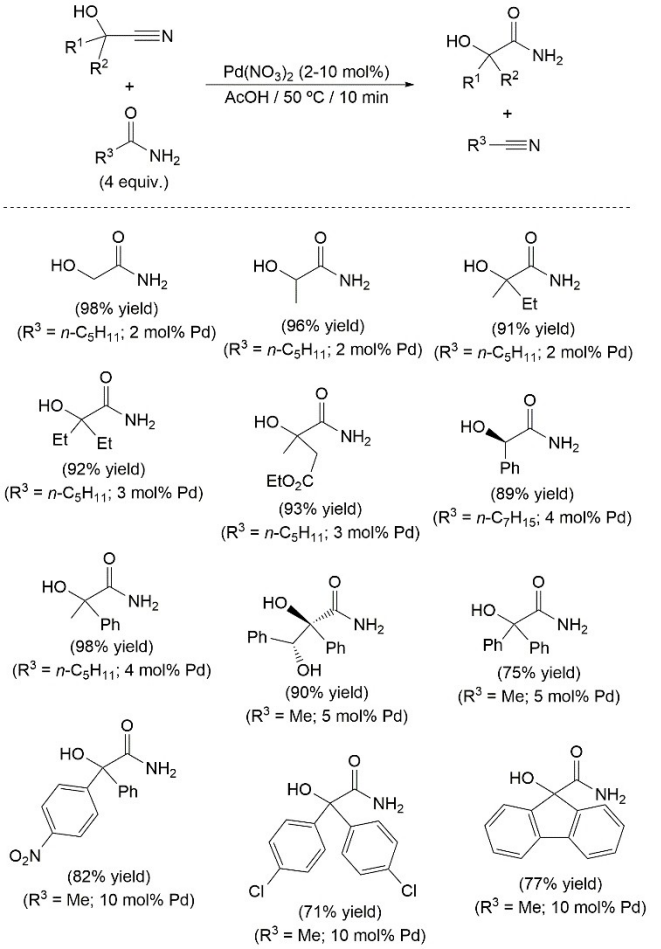
Scheme 12. Silver-catalyzed hydration of acetone cyanohydrin.

generated by decomposition of the NPs in the presence of the cyanohydrin and dissolved oxygen, was actually responsible for the catalytic activity observed. This hypothesis was confirmed with the use of the commercially available $K[Ag(CN)_2]$ salt, which catalyzed the hydration process with an effectiveness comparable to that of the Ag-PTA NPs (see Scheme 12).

In a subsequent study, Tyler and co-workers reported the quantitative hydration of glycolonitrile and lactonitrile at r.t. employing Pt NPs, which showed to be relatively resistant to inhibition by cyanide.[26] In fact, experiments carried out in the presence of KCN showed that complete poison of the NPs only occurs when a large excess of KCN is added to the medium, a result that contrasts with the typical behavior of homogeneous catalysts, where 3 equivalents of cyanide are enough to render the catalyst completely inactive.[14,27] Also of note is the fact that, when acetone cyanohydrin was employed as substrate, 2-hydroxyisobutyramide was formed in a remarkable 30% yield before the cyanohydrin decomposed entirely.[26]

Finally, a very recent work by Naka and co-workers deserves to be particularly highlighted since they were able to develop a protocol for the conversion of both aldehyde and ketone cyanohydrins into α-hydroxyamides applying a transfer hydration strategy.[28] As shown in Scheme 13, the process was conducted in acetic acid at 50 °C, employing $Pd(NO_3)_2$ as the catalyst and a primary amide (hexanamide, octanamide, or acetamide) as the water donor. Under these conditions, transfer of the water molecule from the amide to the cyanohydrin was very fast (10 min), not giving time for the decomposition of the substrate into the corresponding carbonyl compound and HCN, and consequently the poisoning of the palladium catalyst, to occur. An amide/substrate ratio of 4:1 was systematically employed and the amide $R^3C(=O)NH_2$ reagent was specifically chosen in order to facilitate in each case the separation of the final α-hydroxyamide product from the $R^3C(=O)NH_2$ excess and the nitrile $R^3C{\equiv}N$ formed. Regarding the Pd loading employed, it was just adjusted according to the stability of the cyanohydrins, increasing from 2 to 10 mol% with the les stable ones (those derived from aromatic ketones).

The synthetic potential of this unprecedentedly broad scope protocol was nicely illustrated with the derivatization of the antihyperlipidemic drug fenofibrate, a benzophenone derivative functionalized with ester, ether, and chloride groups, by sequential hydrocyanation and Pd-catalyzed transfer hydration



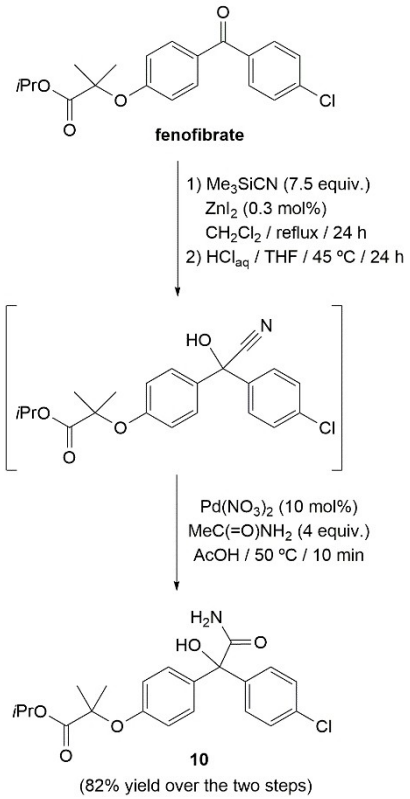
Scheme 13. Pd-catalyzed transfer hydration of cyanohydrins with amides.

(see Scheme 14). The α-hydroxyamide product **10** was selectively obtained in 82% isolated yield over the two steps.[28]

3. β-Hydroxyamides

β-Hydroxyamides are important building blocks in heterocyclic chemistry employed, for example, in the preparation of β-lactams,[29] oxazolidinones,[30] 1,4-diazepanes,[31] azetidines[32] or pyrrolidines.[33] Chiral β-hydroxyamides are also useful ligands for asymmetric catalysis[34] and key intermediates in the synthesis of a number of pharmacologically active compounds such as levamisole (immunomodulating agent with anthelmintic properties),[30a] fluoxetine (antidepressant drug marketed under the trade name Prozac®)[35] and GABOB ((*R*)-γ-amino-β-hydroxybutyric acid; anticonvulsant agent)[30c] (see Figure 4).

Different synthetic approaches have been designed in order to obtain β-hydroxyamides, with the amidation of β-hydroxyacids and esters,[36] the aldol reaction of amide enolates with carbonyl compounds (aldehydes, ketones or acylsilanes),[37] the reduction of β-ketoamides,[38] the ring opening of α,β-epoxy carboxamides,[39] and the catalytic addition of ynamides to ketones[40] being the most commonly employed. However, most



Scheme 14. Derivatization of fenofibrate through a hydrocyanation/transfer hydration sequence.

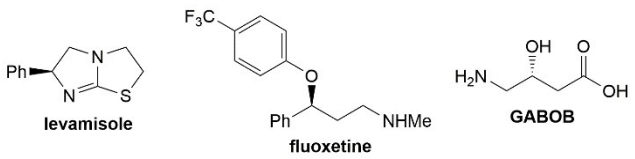
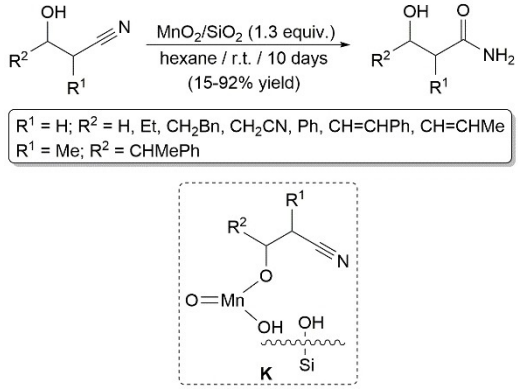


Figure 4. The structures of levamisole, fluoxetine and GABOB.

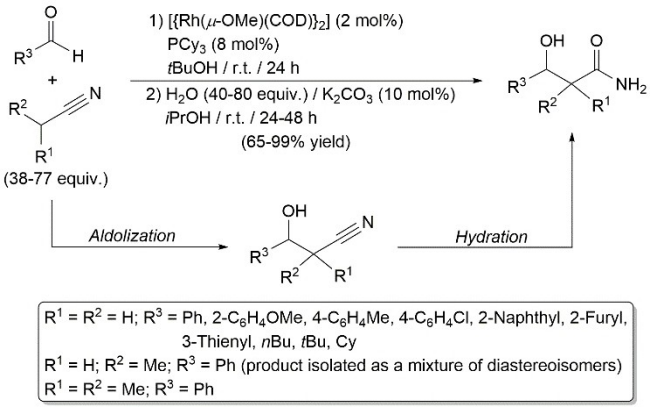
of these synthetic routes are not appropriate for the preparation of primary β-hydroxyamides, the access to this particular class of compounds being usually achieved by hydration of the corresponding β-hydroxynitriles. Such hydration processes have been reported employing classical acid/base approaches,[30a,35,41] enzymatic catalysis[42] and, to a lesser extent, metal-based catalysts. In this context, the metal-mediated hydration of β-hydroxynitriles was described for the first time by Uguen and co-workers in 1994.[43] They found that stirring mixtures of different β-hydroxynitriles with 1.3 equivalents of MnO_2 deposited onto silica gel, in hexane at r.t. for 10 days, results in the formation of the corresponding β-hydroxyamides, which could be isolated in 15–92% yield (see Scheme 15). The addition of water to the reaction medium was no needed, with that absorbed in the gel being enough for the hydration process to proceed. Also of note is the fact that simple nitriles, such as benzonitrile, proved to be much less reactive, suggesting a stronger binding of the β-hydroxynitrile substrates



Scheme 15. Hydration of β-hydroxynitriles using MnO_2 deposited onto silica gel.

to the solid catalyst. In this regard, the transient formation of a manganic ester of type **K** was proposed by the authors. On the other hand, in the context of a general study on the applicability of commercially available amorphous MnO_2 as catalyst for the hydration of nitriles under flow conditions, Ley and co-workers subsequently reported the synthesis of the parent compound $HOCH_2CH_2C(=O)NH_2$ in 98% yield by passing an aqueous solution of $HOCH_2CH_2C{\equiv}N$ through a column containing MnO_2 heated at 100 °C.[44,45]

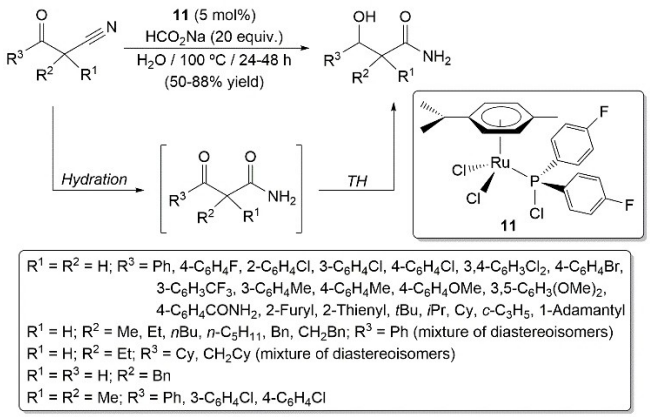
In 2008, Saito and co-workers developed protocols for the aldolization of alkyl nitriles[46] and the hydration of organonitriles[47] employing a catalytic system composed of the rhodium(I) dimer [{Rh(μ-OMe)(COD)}$_2$] (COD = 1,5-cyclooctadiene) and the bulky phosphine ligand PCy_3. Three years later, they nicely combined both processes and developed a straightforward *one-pot* method to generate β-hydroxyamides from aldehydes, alkyl nitriles and water (Scheme 16).[48] Critical points for the reactions to proceed are: (*i*) the use of anhydrous conditions during the aldolization step, (*ii*) removal of any volatile component (the excess of the nitrile, the *t*BuOH solvent and the residual COD) once the intermediate β-hydroxynitriles



Scheme 16. Rh(I)-catalyzed synthesis of β-hydroxyamides from aldehydes and nitriles through an aldolization/hydration sequence.

are formed, and (*iii*) the addition of a catalytic amount of Na_2CO_3 in the hydration step. The latter was carried out in a water/2-propanol mixture and it does not proceed to a large extent in the absence of Na_2CO_3. According to the authors trace amounts of carboxylic acids are generated from the aldehydes during the aldolization reaction that poison the rhodium catalyst if they are not properly neutralized, hence the need for a base. Concerning the scope of the process, it was conveniently confirmed for the aldehyde partner (both aromatic, heteroaromatic and aliphatic aldehydes were tolerated), but with regard to the nitrile only three representatives were screened (acetonitrile, propionitrile and isobutyronitrile). Regardless of this last point, the method resulted effective for the preparation of primary β-hydroxyamides featuring diverse substitution patterns, its main drawback being the large excess of the nitrile required (38–77 equivalents per mol of aldehyde).

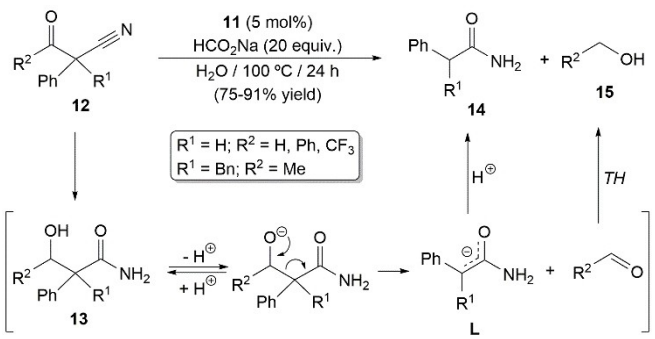
In the context of our studies on the ruthenium-catalyzed hydration of nitriles, we developed in 2016 the first non-enzymatic catalyst, *i.e.* the half-sandwich chlorophosphine-ruthenium(II) complex [$RuCl_2(\eta^6$-*p*-cymene){$P(4\text{-}C_6H_4F)_2Cl$}] (**11**), capable to hydrate β-ketonitriles in a selective manner, process that proceeds under mild conditions (40 °C) in pure water and without the assistance of any acidic or basic additive.[49] Based on this result and the known ability of ruthenium(II) complexes to catalyze the reduction of carbonyl compounds in water by transfer hydrogenation (TH) with sodium formate, we further exploited the utility of **11** with the development of a procedure for the direct conversion of β-ketonitriles into β-hydroxyamides combining in *one-pot* both catalytic reactions.[50]



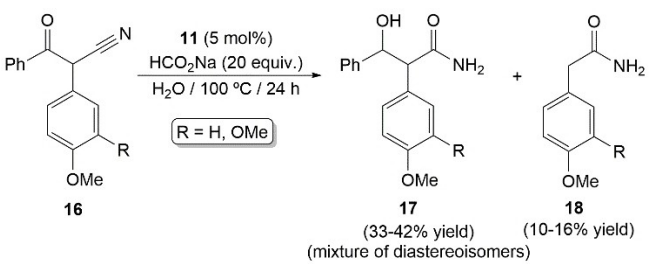
Scheme 17. Catalytic synthesis of β-hydroxyamides from β-ketonitriles.

As shown in Scheme 17, refluxing conditions, excess of HCO_2Na (20 equivalents with respect to the β-ketonitrile substrate) and long reaction times were needed to facilitate the reduction of the C=O bond of the corresponding β-ketoamide intermediates (rate-limiting step of this tandem process). The scope of the reaction was very high and allowed the preparation of a large number of β-hydroxyamides featuring different substitution patterns in α and γ position. However, a limitation was found regarding the use β-ketonitriles substituted in α position with an aryl group, such as compounds **12** in Scheme 18, since the corresponding β-hydroxyamide products **13** decompose through a retro-aldol type reaction under the basic conditions employed.[50b] At the end of the reactions, the cleaved amides **14** were isolated and alcohols **15** were detected in the crudes by gas chromatography before solvent removal. The easy cleavage of the C–C bond in the α-phenyl-β-hydroxyamides **13** was reasoned in terms of the stabilizing effect that the electronic delocalization of the negative charge, by conjugation with the aromatic ring, exerts on the amide enolate intermediate **L** (see Scheme 18). This hypothesis was supported by the fact that introduction of electron-donor groups on the aromatic ring disfavors the retro-aldol reaction, as exemplified with the β-ketonitriles **16** from which the α-aryl-β-hydroxyamides **17**, along with cleaved amides **18**, could be isolated (Scheme 19).[50b]

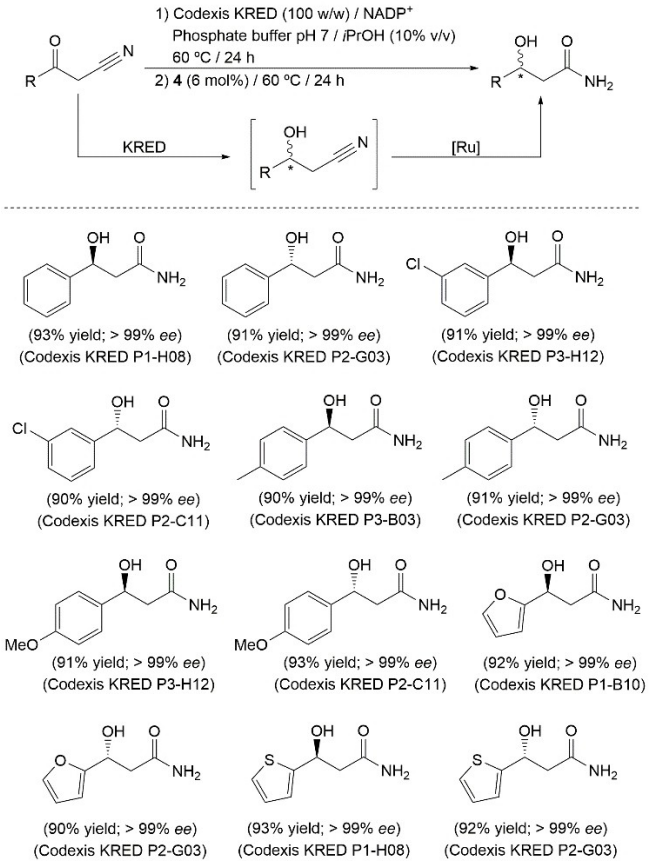
In a subsequent study, we also succeeded in the *one-pot* conversion of β-ketonitriles into optically pure β-hydroxyamides, through a bioreduction/hydration cascade process, by sequential combination of commercial engineered ketoreductases (included in the Codex® KRED Screening Kit from Codexis) with the bis(allyl)-ruthenium(IV) derivative [$RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(PMe_2OH)$] (**4**; see Scheme 9).[51] Unlike [$RuCl_2(\eta^6$-*p*-cymene){$P(4\text{-}C_6H_4F)_2Cl$}] (**11**), complex **4** was found to be fully compatible with the KREDs and the reaction conditions required for the enzymatic reduction of the substrates to proceed, thus allowing to catenate a ruthenium-catalyzed hydration of the resulting β-hydroxynitriles without the requirement of purification steps. The results obtained employing a family of aromatic and heteroaromatic α-unsubstituted β-ketonitriles are shown in Scheme 20. Given the exquisite stereoselectivity exhibited by the KREDs during the carbonyl



Scheme 18. Behavior of the α-phenyl-β-ketonitriles **12** in the Ru-catalyzed hydration/TH process.



Scheme 19. Ru-catalyzed hydration/TH of α-aryl-β-ketonitriles **16**.



Scheme 20. Conversion β-ketonitriles into optically pure β-hydroxyamides through a bioreduction/hydration cascade process.

group reduction, the final β-hydroxyamide products could be obtained with $>99\%$ *ee*, in very high yields ($\geq 90\%$) and, more importantly, in both enantiomeric forms just by selecting the appropriate enzyme.[52]

In addition to the examples given in Scheme 20, good results were also obtained starting from α-substituted β-ketonitriles since KREDs are capable to promote effectively the dynamic reductive kinetic resolution (DYRKR) of this type of molecules.[53] As shown in Figure 5, the resulting β-hydroxyamide products were produced with high diastereo- and enantioselectivity levels, not observing the racemization of any stereogenic center of the chiral β-hydroxynitrile intermediates during the Ru-catalyzed hydration step.[51]

Moreover, we demonstrated the usefulness of this sequential chemoenzymatic protocol with the total synthesis of the naturally occurring alkaloids (*S*)-(+)-tembamide (active against HIV) and (*R*)-(−)-aegeline (hypoglycemic activity) using the single enantiomers of the β-hydroxyamide **19**, generated as depicted in Scheme 20, as starting materials (Scheme 21).[51] The synthetic routes involved the initial Hoffman rearrangement of **19** promoted by iodobenzene diacetate, followed by basic hydrolysis of the resulting oxazolidinones **20**, and final acylation of the β-amino alcohols **21** with the appropriate acid chloride. The desired (*S*)-(+)-tembamide and (*R*)-(−)-aegeline products were isolated in high overall yield (77% or 73%, respectively) and in an enantiopure manner ($>99\%$ *ee* in both cases).

In addition to these studies, taking advantage of the ability of the $Pd(OAc)_2/PPh_3$ system to promote the transfer hydration of nitriles with acetaldoxime,[54] Kim and co-workers reported the synthesis of the primary β-hydroxyamides **23** employing as substrates different aromatic, heteroaromatic and aliphatic Baylis-Hillman adducts of acrylonitrile, *i.e.* compounds **22** (Scheme 22).[55] The reactions, which were carried out in refluxing ethanol with a $Pd(OAc)_2$ loading of 10 mol% and two equivalents of acetaldoxime, afforded amides **23** in 70–84% yield.

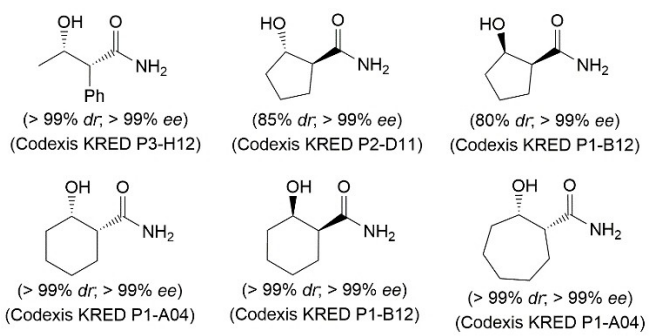
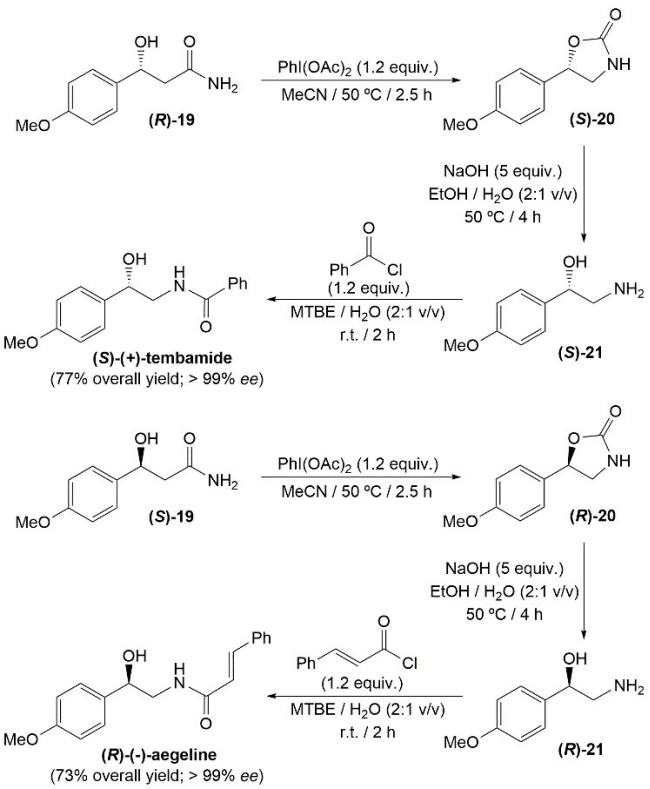
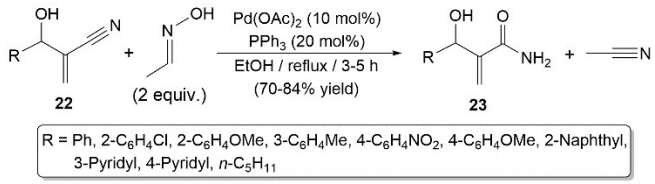


Figure 5. Structure of the chiral α-substituted β-hydroxyamides generated through the sequential DYRKR/hydration process.



Scheme 21. Total synthesis of (*S*)-(+)-tembamide and (*R*)-(−)-aegeline using enantiomers of the chiral β-hydroxyamide **10** as starting materials.



Scheme 22. Pd-catalyzed transfer hydration of β-hydroxynitriles **22**.

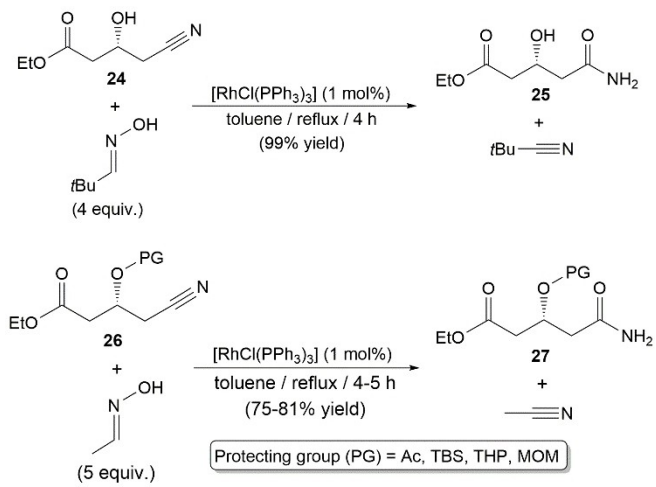
Transfer hydration of the chiral β-hydroxynitrile **24** with pivalaldoxime catalyzed by the Wilkinson's catalyst [$RhCl(PPh_3)_3$] in refluxing toluene was additionally described by Chang, Lee and co-workers (Scheme 23).[56] The resulting β-hydroxyamide **25** was obtained in almost quantitative yield without observing racemization during the reaction. In the same work, clean conversion of the related *O*-protected nitriles **26** into amides **27** was also successfully accomplished employing acetaldoxime as the water source.

4. Ureas

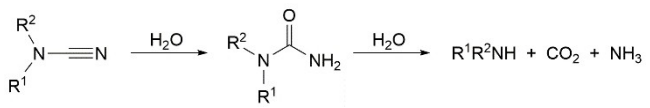
Substituted ureas are relevant moieties in bioactive compounds, such as agrochemicals and pharmaceuticals.[57] The diverse and versatile structural properties of ureas also make them useful reagents and organocatalysts in organic chemistry, as well as interesting scaffolds for supramolecular chemistry and anion recognition.[58] Urea derivatives have been traditionally synthesized by methodologies based on the reaction of amines with phosgene, carbon monoxide or isocyanates, which have tremendous toxicological and environmental problems.[59] Several safer and cleaner approaches employing less accessible phosgene substitutes have appeared during the last decades,[60] and significant efforts have also been devoted to develop efficient catalytic systems to access substituted ureas from CO_2 and amines, but harsh reaction conditions are usually required.[61,62] Substituted ureas can be alternatively generated by hydration of readily accessible cyanamides,[62] an attractive process considering its simplicity and complete atom economy (Scheme 24).

However, most of the protocols for the hydration of cyanamides described so far in the literature make use of Bronsted acids and bases, which require of a careful control of the reaction conditions to avoid the competing hydrolysis of the urea products (see Scheme 24).[63,64] It should also be noted at this point that, unlike classical aromatic and aliphatic nitriles, biocatalytic approaches for the hydration of cyanamides are extremely rare and restricted to the H_2N–C≡N to H_2N–C(=O)–NH_2 conversion.[65] Surprisingly, despite the well-known fact that the reactivity of cyanamides towards nucleophiles is drastically enhanced upon coordination to a transition metal,[66,67] metal-catalyzed protocols for the hydration of cyanamides into ureas have only came to the fore during the last decade. The first one was described by Nasrollahzadeh in 2014 making use of TiO_2 nanoparticles (NPs) in conjunction with formic acid (Scheme 25).[68] The reactions, which were performed in water at room temperature, allowed the rapid and selective conversion of different aromatic monosubstituted cyanamides into the corresponding *N*-aryl ureas, which were isolated in 92–96% yield. Blank experiments showed that the combined use of TiO_2 and HCO_2H is crucial for the hydration process to proceed (no reaction took place in the absence of HCO_2H and modest conversions after 24 h were observed when formic acid was employed alone), suggesting that the nitrile group of the substrates is activated towards the addition of water by both reagents. Also of note is the fact that the TiO_2 NPs could be easily recovered by filtration at the end the reactions and successively reused 5 times without significant loss of activity.

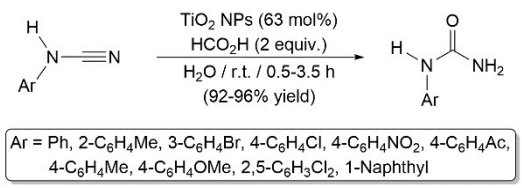
Further studies by Nasrollahzadeh and co-workers demonstrated the utility of silver NPs (unsupported[69,70] or supported on cow bones powder[71]) as selective and recyclable catalysts (up to 5 consecutive runs) for the hydration of related *N*-aryl monosubstituted cyanamides. They were able to operate in pure water[69] or in aqueous extracts of plants (*Gongronema latifolium*[70] and *Myrica gale L.*[71]), the latter acting also as green reductants and stabilizing agents for the *in situ* generation of



Scheme 23. Rh(I)-catalyzed transfer hydration of nitriles **24** and **26**.



Scheme 24. Hydration and hydrolysis reactions of cyanamides.



Scheme 25. Hydration *N*-aryl cyanamides in water catalyzed by TiO_2/HCO_2H.

the Ag nanoparticles by reduction of $AgNO_3$, without the requirement of any acidic or basic additive. However, refluxing conditions were in all cases needed to obtain the desired *N*-aryl ureas in high yields. The magnetic nanocatalysts **28**, consisting of a cationic tetramine-palladium(II) complex anchored to the surface of silica-coated ferrite nanoparticles (see Figure 6), is an additional example of an heterogeneous catalyst capable to hydrate *N*-aryl monosubstituted cyanamides.[72] In the absence of additives, the reactions proceeded cleanly in water only when refluxing conditions were employed. Nonetheless, the authors found that the addition of formic acid to the medium allows to carry out the reactions at room temperature with almost the same effectiveness (yields around 90% in all the cases after 0.5–2.5 h). Separation of catalyst **28** from the urea products could be in this case accomplished with the aid of an external magnet and its reusability conveniently confirmed (up to 6 consecutive runs).

Very recently, our group successfully accomplished the hydration of cyanamides under homogeneous conditions employing the phosphinous acid-based complexes [$MCl_2(\eta^6$-*p*-cymene)(PMe_2OH)] (M = Ru (**3**), Os (**29**)).[73] Both of them were able to operate in pure water, under relatively mild conditions (40–70 °C) and in the absence of additives. In addition, they showed a broad substrate scope, being able to hydrate in a selective manner a large number of aromatic and aliphatic mono- and disubstituted cyanamides as well as the parent H_2N–C≡N. In almost all the cases, the osmium complex **29** featured a superior reactivity in comparison to that of its ruthenium counterpart **3**, allowing the access to the desired substituted ureas in high yields (see Scheme 26).

Interestingly, the reaction rates observed in the hydration reactions of cyanamides with complexes [$MCl_2(\eta^6$-*p*-cymene)(PMe_2OH)] (M = Ru (**3**), Os (**29**)) were faster than those involving classical nitriles R–C≡N (R = aryl or alkyl group),[21,74] a fact that could be rationalized by means of computational DFT studies. Thus, the calculations indicated that the higher reaction rates observed with the cyanamide substrates are associated with the inductive effect exerted by the NR^1R^2 unit on the C≡N carbon, which favors the generation of the corresponding five-membered metallacycle **M**, key intermediate in the catalytic cycle, by intramolecular nucleophilic attack of the OH group of the phosphinous acid ligand to this carbon (Scheme 27).[73]

On the other hand, metal-catalyzed transfer hydration strategies have also been employed to achieve the conversion of cyanamides into ureas. For example, Kim and co-workers exploited the ability of $InCl_3$ to catalyze the transfer hydration of nitriles with acetaldoxime[75] to synthesize different mono- and disubstituted areas from the corresponding cyanamides.[76] As shown in Scheme 28, the reactions proceeded cleanly in toluene at r.t. or 40 °C, using 2 equivalents of MeCH=NOH per mole of substrate.

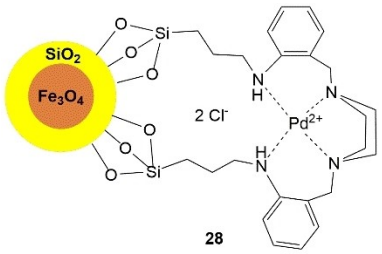
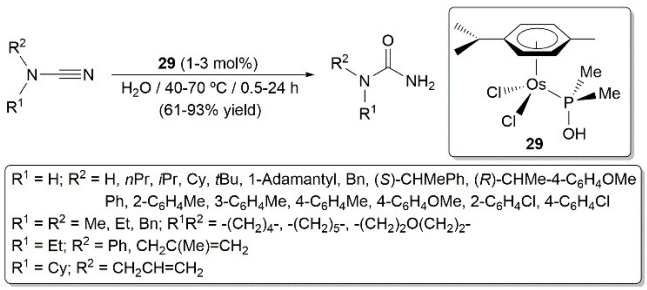
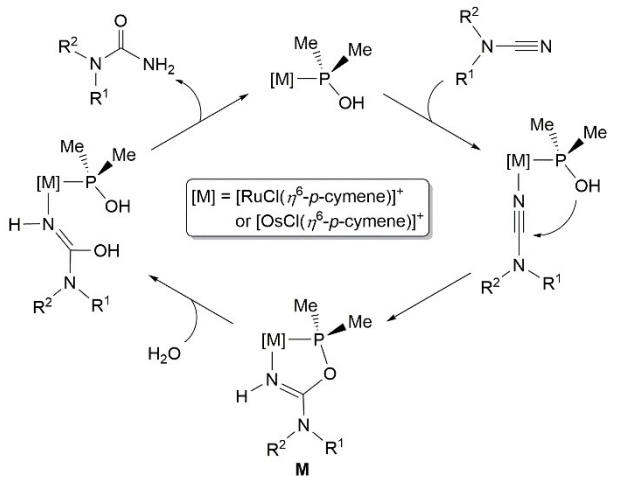


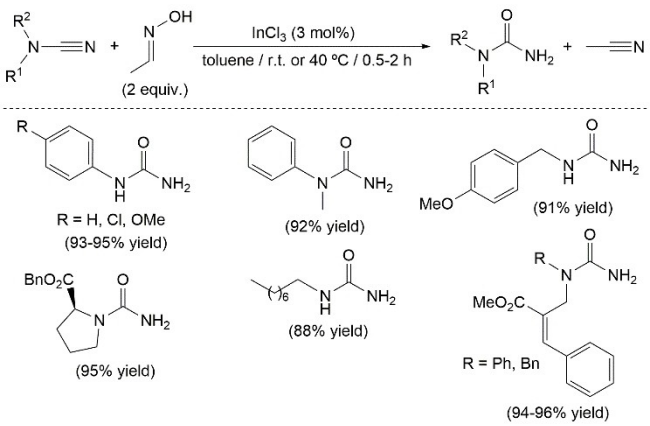
Figure 6. Structure of the magnetic nanocatalyst **28**.



Scheme 26. Catalytic hydration of cyanamides using the Os(II) complex **29**.



Scheme 27. Catalytic cycle for the hydration of cyanamides catalyzed by complexes [$MCl_2(\eta^6$-*p*-cymene)(PMe_2OH)] {M = Ru (**3**), Os (**29**)}.



Scheme 28. $InCl_3$-catalyzed transfer hydration of cyanamides with acetaldoxime.

Related transfer hydration reactions of cyanamides with acetaldoxime as water surrogate catalyzed by CeO_2 (5 mol%) and CuO (10 mol%) NPs in refluxing ethanol were additionally reported by the groups of Sajadi and Nasrollahzadeh.[77,78] The corresponding ureas were obtained in high yields ($\geq$83%) and short times (2 h) employing cyanamide/acetaldoxime molar ratios of 1:1 and 1:1.5, respectively. After completion of the reactions, both nanocatalysts could be easily recovered by filtration and reused without appreciable loss of effectiveness (up to 5 consecutive runs).

5. Concluding Remarks

In this Minireview article, the state of the art regarding the synthesis of three relevant families of carboxamide ($CONH_2$) containing compounds, *i.e.* α-hydroxyamides, β-hydroxyamides and ureas, through metal-catalyzed C≡N bond hydration and transfer hydration strategies has been summarized. Concerning the α-hydroxyamides, their access by catalytic hydration of cyanohydrins has been for long time considered as the main challenge in the field due to the relatively low stability of the cyanohydrins in solution. Unlike other organonitriles, which can be hydrated at high temperatures, cyanide-resistant metal catalysts capable to operate under mild conditions and in short times are required in the case of cyanohydrins. In this regard, some promising results have been achieved employing bifunctional homogeneous catalysts with cooperative ligands and metal nanoparticles. Nonetheless, catalytic systems featuring a wide scope have not been yet disclosed, the most general approach reported to data involving the Pd-catalyzed transfer hydration with amides. In the case of β-hydroxyamides, different catalytic systems for the hydration and transfer hydration of β-hydroxynitriles can be currently found in the literature, the most outstanding results in the field being probably those described by our group combining KREDs with ruthenium complexes which allowed the access to a broad range of enantiopure β-hydroxyamides from readily accessible β-ketonitriles. Finally, recent reports have demonstrated the utility of both heterogeneous and homogeneous catalysts for the selective synthesis of substituted ureas from cyanamides under mild conditions, thus offering convenient alternatives to the classical methodologies based on the use of strong Bronsted acids and bases. Given the synthetic relevance of the carboxamide compounds herein considered, further studies dealing with the discovery of more efficient catalysts are expected in the near future, with particular emphasis in homogeneous systems which have provided up to now the wider scope protocols to access these molecules.

Acknowledgements

Financial support by the Spanish Ministry of Economy, Industry and Competitiveness is acknowledged (MINECO project CTQ2016-75986-P).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Heterogeneous catalysis · Homogeneous catalysis · Hydration · Hydroxyamides · Nitriles · Reaction mechanisms · Ureas

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Manuscript received: May 13, 2021
Revised manuscript received: June 21, 2021
Accepted manuscript online: June 22, 2021