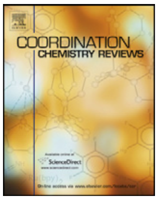
Coordination Chemistry Reviews 255 (2011) 949–974

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr



Review

Frontiers in catalytic nitrile hydration: Nitrile and cyanohydrin hydration catalyzed by homogeneous organometallic complexes

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Contents

ARTICLE INFO

Article history:
Received 2 July 2010
Accepted 25 August 2010
Available online 24 September 2010

Keywords:
Nitrile hydration
Acrylic monomers
Acetone cyanohydrin
Homogeneous catalysis
Nitrile hydratase

ABSTRACT

Acrylic monomers are a significant part of the global economy, contributing to the manufacture of over a billion tons of diverse polymeric consumer products every year. The development of more efficient, greener methods to manufacture this highly demanded class of compounds is an important goal in the realization of a sustainable chemical industry. The pursuit of environmentally benign production processes has inspired a rich body of industrial and academic research on methods for the catalytic hydration of nitriles, and this review surveys both established and newer methods of generating acrylic amides, acids, and esters from nitrile and cyanohydrin substrates. The review also examines synthetic and mechanistic studies of homogeneously catalyzed nitrile hydration reactions with an emphasis on explicating the parameters that impact catalyst performance. The final section is a discussion of catalyst properties, gleaned from the mechanistic studies, that will be useful in designing the next generation of nitrile hydration catalysts.

1. Introduction

The catalytic hydration of nitriles is an efficient, atom economical route to amides, and therefore it is an important transformation in current and future sustainable chemical technologies. Perhaps

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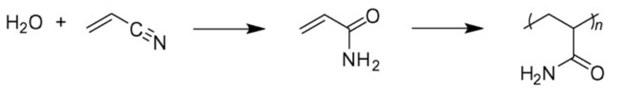
doi:10.1016/j.ccr.2010.08.018



Scheme 1. Hydration of acrylonitrile followed by polymerization to acrylamide.

the greatest potential impact for green catalytic nitrile hydration processes is in the synthesis of acrylic amides, esters, and acids, which are used to make an impressive range of polymeric consumer products [1,2]. One such polymer is polyacrylamide, which is prepared by the polymerization of acrylamide (Scheme 1) and is used in water treatment [1–5], gel electrophoresis, paper strengthening, and in adhesives.

The economic importance of acrylamide is attested to by the huge quantities that are manufactured each year. In 2001, two hundred thousand metric tons of acrylamide were produced, and the market for acrylamide was projected to continue increasing at a rate of 4% per year [5]. A substantial portion of acrylamide is converted to acrylic acid and acrylic esters [1,2]. Polyacrylic acids are super absorbent polymers used in diapers and other hygiene products. Acrylic acids are also copolymerized with other alkyl acrylates, such as ethyl and *n*-butyl acrylates, for the production of acrylic coatings and paints. Methacrylic acid and ester monomers are primarily generated from acetone cyanohydrin (Scheme 2), and they represent an even larger global market, with the annual demand for methacrylic monomers exceeding several million metric tons [1,2].

Unlike the soft polyacrylates, polymethacrylates are typically inflexible due to the rigidity imparted by the methyl groups [2]. Poly(methyl methacrylate), in particular, is a shatterproof, transparent plastic better known as Plexiglas^{TM}. These and other remarkable properties of methacrylic monomers are useful for a plethora of commercial products including windshields, signs, safety glasses, and bathtubs.

All told, acrylic monomers represent a significant part of our global economy, leading to nearly a billion metric tons of polymeric consumer products in the United States alone [2]. A problem, however, is that classical methods of converting nitriles to amides present several disadvantages (e.g., high energy demands, harsh conditions, and the generation of wasteful byproducts). For example, under dilute acidic or basic conditions, nitrile hydration is less energetically favorable than the hydrolysis of the resulting amide, and a mixture of the amide and carboxylic acid is produced [6,7]. Generation of unwanted organic acid compromises the amide yield and also requires energy intensive purification steps. As a result, the classical industrial production of acrylic amides employs concentrated sulfuric acid [1,4]. Hydrolysis of the amide does not occur under these conditions; however, the strongly acidic environment leads to formation of the amide sulfate salt. Subsequent neutralization of the amide sulfate with ammonia affords the amide and ammonium sulfate, which is typically sold as fertilizer. The discovery of efficient Cu transition metal nitrile hydration catalysts (such as Raney Cu [4,8], various mixed metal Cu oxides [9], and Cu(I) and Cu(II) salts [10]) eliminated the need for acidic conditions and the additional processing steps required for conversion of the amide sulfate. However, the use of Cu salts in the industrial production of acrylamide presents several problems [11]: (1) the process typically requires separation of the unreacted acrylonitrile and the Cu salt catalyst from the product stream. (2) The Cu systems require complex preparation and regeneration procedures, which represent unnecessary costs. Furthermore, Cu catalysts are completely inadequate in the hydration of acetone cyanohydrin and cannot be used in the synthesis of methacrylates.

Small improvements in the manufacture of such high demand commercial products can have a huge effect on production costs, retail costs, and the environmental and health risks associated with the processes. As such, efforts toward developing greener and more cost effective methods of synthesizing vinyl amides are ongoing in industry and in academia. The following paragraphs will highlight the latest advances and the lingering challenges in the large-scale synthesis of acrylic monomers. From an academic perspective, considerable progress has been made toward the development and elucidation of homogeneous transition metal catalysts for the regioselective hydration of acrylonitrile and α-hydroxynitriles (commonly referred to as cyanohydrins) to acrylamide and α-hydroxyamides, respectively. Although such homogeneous catalysts are not yet practically useful, investigations of catalytic acrylonitrile and cyanohydrin hydration provide mechanistic insight that may be used to rationally design new, greener routes to acrylic monomers and are therefore a particularly worthy challenge for researchers in the field. A major purpose of this review is to expose the green frontier in the well-studied area of metal-catalyzed nitrile hydration by linking chemical knowledge of the field with the industrial demand for more efficient and environmentally friendly methods of utilizing fossil fuel resources. This review will focus on catalytic nitrile hydration as it pertains to the generation of acrylic amides, esters, or acids and on the exposition of the mechanistic pathways for these reactions. More general reviews of metal-mediated and metal-catalyzed nitrile hydration reactions [7,12–15] and other addition reactions of metal-activated organonitriles [13,16,17] have been published in the past 15 years.

2. New synthetic strategies used to prepare acrylic amides, acids, and esters

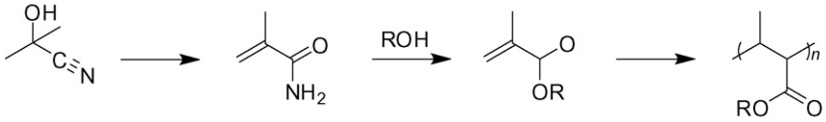
2.1. Biocatalytic routes to acrylic amides and acids

2.1.1. Industrial biotransformation of acrylonitrile

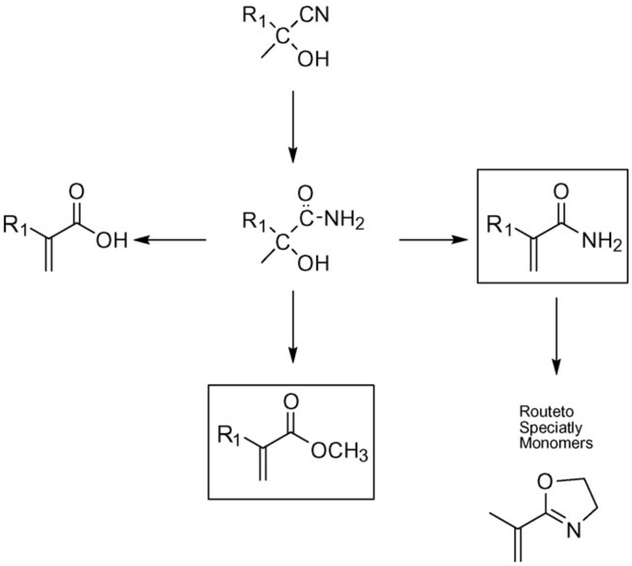
Impressive advances were recently made in the production of acrylamide using immobilized nitrile hydratases (or NHases) [3,11,18–22]. NHases contain non-heme low-spin Fe(III) or non-corrinoid low-spin Co(III) centers and are used by microorganisms to hydrate nitriles exuded from plant biomass for the generation of essential carboxylic metabolites. The benefits of using biocatalysis for commercial production are the high selectivity of the enzymes and the low energy input required. However, enzymes are expensive to isolate and extremely susceptible to product inhibition, making them impractical for batch reactions [11,23]. Nitto Chemical Industry Co., Ltd in Japan was able to circumvent these problems in the production of acrylamide by immobilizing bacterial cells containing NHase in a cationic acrylamide based polymer [3,11]. Using this method, almost quantitative conversion of acrylonitrile is achieved below 10 °C even in the presence of 17.5% acrylamide. The biocatalytic hydration of acrylonitrile is relatively simple and economical compared to Cu catalyzed processes. The usefulness of the biocatalytic technology was demonstrated in the late 1980s, and by 2002 at least six plants had replaced their technology with a similar immobilized enzyme approach.

2.1.2. Efforts to expand the utility of biocatalysis to alkylacrylic monomers

The successful application of microbial NHases in the industrial production of acrylamide demonstrated the potential of biocatalysis in the synthesis of a variety of alkylacrylic monomers via the hydration of alkyl cyanohydrins (Scheme 3). In fact, the use of NHases to promote the hydration of selected cyanohydrins, like lactonitrile and *p*-chloromandelonitrile, has received much attention in the chemical literature [23–30]. A range of NHases (including those belonging to the genera *Rhodococcus* [27,28], *Corynebac-*



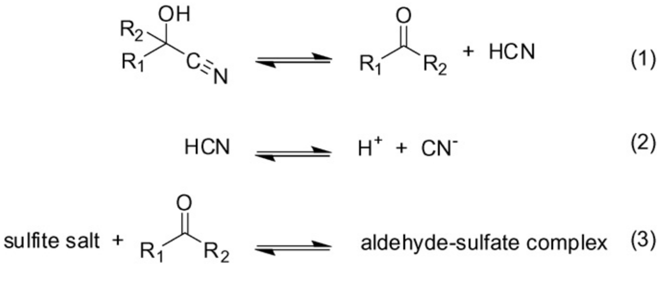
Scheme 2. Synthesis of poly(methacrylic esters) from acetone cyanohydrin.



Scheme 3. Routes to alkylacrylic monomers starting from alkyl cyanohydrins.

terium [23], *Pseudomonas* [26], *Arthrobacter* [23], *Alcaligenes* [30], *Brevibacterium* [23], and *Nocardia* [23]) have been used, often in combination with amidase, to prepare α-hydroxyamides and carboxylic acids. Efficient reactivity and optical resolution was noted in several cases, and the use of NHases was applied to the enantioselective syntheses of fine chemicals containing α-hydroxyamide and α-carboxylic acid moieties. For example, nitrilase biocatalysts were used to produce (R)-mandelic acid and (R)-3-chloromandelic acid in high yields [31]. NHases have been used for the stereoselective conversion of (R,S)-(±)-ibuprofen nitrile to (S)-(+)-ibuprofen and to convert (±)-2-arylpropionitriles to the corresponding (S)-amides [32].

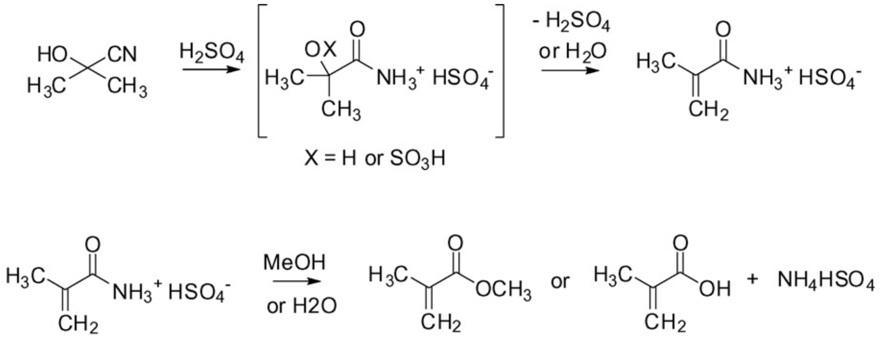
Unfortunately, application of such advancements to the large-scale enzymatic synthesis of alkylacrylates is still under development. One reason for the delay is that the activity of NHases varies greatly with the exact nature of the cyanohydrin. Several reports note an acute sensitivity of NHase enzymes and microbial cells toward cyanohydrin substrates and/or their dissociation products (aldehydes and HCN) [23]. To suppress enzyme poisoning, Tamura of the Nitto Chemical Industry Co., Ltd developed a process in which a constant, low concentration of substrate was maintained automatically by using a cyano ion detector in combination with a regulated cyanohydrin dispenser [23]. The concentration of substrate could be determined from the cyanide concentration using a calibration curve because dissociation equilibria (Scheme 4) were established under optimal microbial reaction conditions at a constant pH, temperature, and ionic strength. In addition to controlling substrate concentration, the toxicity of the aldehyde dissociation product was mitigated by adding sulfite salts to the reaction mixture, thereby forming an innocuous aldehyde-sulfate complex that existed in equilibrium with the substrate and dissociation products. Using this process, over 40 substituted cyanohydrins could be hydrated, yielding up to 1.5 M concentrations of α-hydroxyamides and α-hydroxycarboxylic acids with excellent optical purity (greater than 95% e.e. in most cases). Interestingly, acetone cyanohydrin was explicitly omitted from the list of viable substrates.



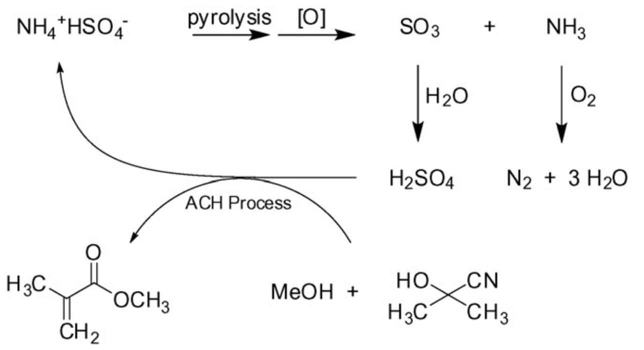
Scheme 4. Equilibria in a cyanohydrin hydration reaction mixture due to dissociation of a (1) cyanohydrin and (2) hydrocyanic acid, as well as the (3) formation of an aldehyde-sulfate complex.

2.2. Routes to methacrylic monomers

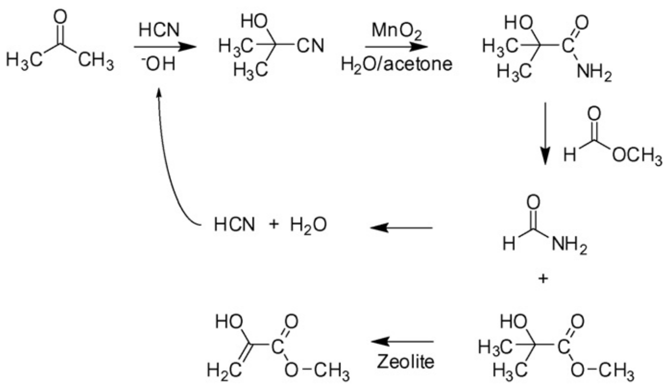
Due to the poor activity of Cu salts and NHase enzymes in the synthesis of methacrylic amides, most industrial practices for the generation of methacrylate monomers still rely on concentrated sulfuric acid. Other methods of obtaining methacrylates from acetone cyanohydrin include the Mitsubishi process, which utilizes the heterogeneous MnO_2 catalyst, and borate salt-catalyzed nitrile hydration. These methods are discussed below.



Scheme 5. The ACH process for synthesizing methyl methacrylate (MMA) and methylacrylic acid (MAA) using concentrated sulfuric acid.



Scheme 6. Recycling process for ammonium hydrogen sulfate (AHS).



Scheme 7. Mitsubishi process for the manufacture of MMA and recycling of HCN.

2.2.1. *The ACH process*

The primary industrial process by which methacrylates are synthesized is the ACH process, shown in Scheme 5 [1]. In this route, acetone is reacted with HCN to form acetone cyanohydrin (ACH), which is then reacted with sulfuric acid at moderate temperature to form the sulfuric ester of 2-hydroxy-2-methylpropionamide. Heating leads to the elimination of sulfuric acid (or water) and the formation of methacrylamide sulfate. In this process, the amide sulfate salt is then either hydrolyzed with water to form methacrylic acid (MAA), or it is esterified with a mixture of water and methanol to form methyl methacrylate (MMA) in very high yield (>92%). However, the mass balance includes undesired sulfonates, oligomers, polymers, and ammonium hydrogen sulfate (AHS) generated as a result of the strongly acidic reaction conditions.

The production of AHS is a major economic and environmental drawback of a large-scale sulfuric acid mediated process because its disposal requires additional processing steps. The excess sulfuric acid used in the synthesis generates about 2.5 kg of AHS per kg of methacrylate product. The most common disposal solution is to pyrolyze the AHS at around 1000 °C (Scheme 6). Pyrolysis releases SO_2, which upon oxidation to SO_3 is absorbed into water to form sulfuric acid. The sulfuric acid is then reused in the ACH process. This process is highly energy intensive and consumes copious amounts of natural gas as fuel. Ammonia is also formed but is not recovered because under these conditions it reacts with oxygen to form N_2. In an alternative approach, the AHS is neutralized with ammonia to form ammonium sulfate, which has use as a fertilizer. As mentioned, there is considerable expense and effort associated with both of these methods, and so the elimination of AHS would allow for considerable savings and improvement in the industrial production of methacrylates. Consequently, there is a strong drive by methacrylate producers to find a replacement to the ACH process that does not involve sulfuric acid.

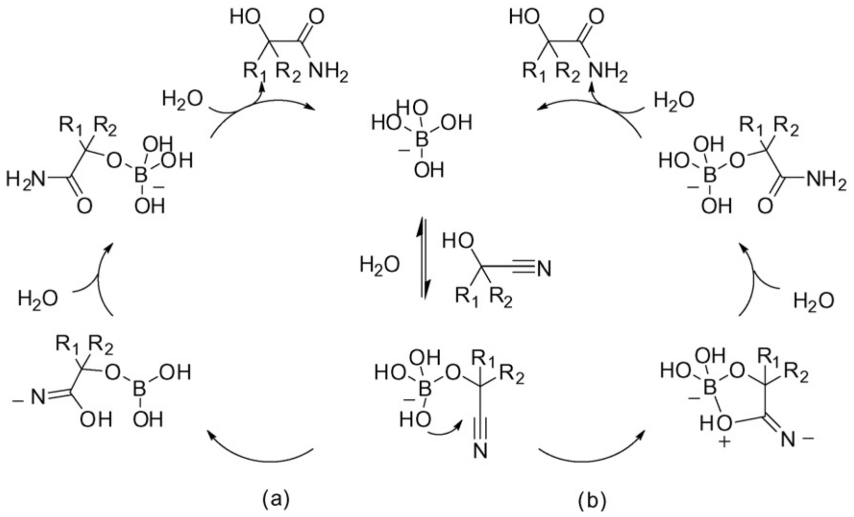
2.2.2. *Routes to methacrylates based on other (non-nitrile) feedstocks*

Several methacrylate manufacturers have opted to develop methods based on organic feedstocks other than nitriles. Because this review focuses on frontiers in catalytic nitrile hydration, non-nitrile involving pathways are discussed only briefly. Among the new methods that have been proposed for the production of methacrylates are (i) a process using a direct catalytic oxidation of isobutylene or *t*-butanol, (ii) the ammoxidation of *t*-butanol, (iii) a method using ethylene, CO, and formaldehyde, originally developed by BASF for making methacrolein and later refined by ICI, Ineos and Lucite for making MMA and MAA directly [33], (iv) a route involving the direct oxidative esterification of methacrolein, developed by Asahi Chemical Co., and (v) a process for the direct carbonylation of propyne (which is not viable due to a lack of sufficient feedstock). Despite considerable promise, each of these new processes has disadvantages that keep them from being widely adopted [1].

2.2.3. *Successful acid-free hydration of acetone cyanohydrin*

2.2.3.1. Mitsubishi's clever strategy to recycle HCN. Mitsubishi Gas Chemical Company developed a sulfuric acid-free ACH process using MnO_2 [34,35], and it is currently being used in the manufacture of methyl methacrylate [1]. In the Mitsubishi process (Scheme 7), the hydration of ACH to α-hydroxyisobutyramide (HIBAM) is carried out catalytically using a slurry of MnO_2 in a water/acetone mixture. Methyl formate is used to esterify HIBAM to α-hydroxyisobutyrate, which generates formamide as a byproduct. Subsequent dehydration of α-hydroxyisobutyrate gives MMA, and heating of formamide releases HCN and water. The HCN generated is then recycled in the production of ACH. This process is advantageous for two reasons: (1) the use of MnO_2 eliminates the generation of AHS. (2) The use of methylformate allows the nitrogen in HIBAM to be captured as formamide and recycled into HCN. Interestingly, MnO_2 must be treated to modify its structure for optimal activity, which adds to the overall manufacturing cost [36]. Furthermore, even with treatment, the efficacy of the resulting catalyst fluctuates from batch to batch, resulting in inconsistent product yields [35]. Because mechanistic investigations of heterogeneous catalytic systems are often ambiguous, the exact factors that affect the reactivity of these complexes toward cyanohydrins have not been delineated. The reaction yields are improved by performing the reaction in acetone cosolvent; however, the use of excess acetone also increases production costs. Overall, the engineering costs associated with setting up this new ACH process render it less cost effective than the current sulfuric acid chemistry employed.

2.2.3.2. Boron-catalyzed cyanohydrin hydration. Noteworthy examples of cyanohydrin hydration catalyzed by borate salts have also been disclosed in patents [36] and in the chemical literature [37,38] but have not yet proven industrially viable. Borate salts are quite reactive toward cyanohydrins under alkaline conditions. Mechanistic investigations of the borates suggest that they activate the cyanohydrin by reacting with the cyanohydrin alcohol group to form a borate ester (Scheme 8) [38]. The activated cyanohydrin is then hydrated either by transfer of a boron-bound hydroxide (Scheme 8a), or by nucleophillic attack of a borate hydroxy group, resulting in formation of a five-membered intermediate (Scheme 8b). Discerning between these two mechanistic pathways has proven difficult because both mechanisms involve negatively charged intermediates. Nonetheless, reaction of the hydroxy group with the nitrile carbon is proposed to be rate determining, and the entropy of activation may distinguish between formation of the five-membered ring and hydroxide transfer. Activation parameters



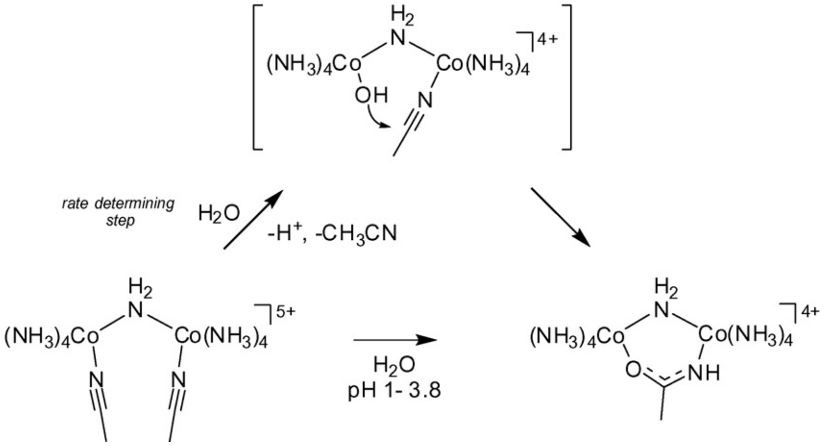
Scheme 8. Proposed mechanisms for borate-catalyzed hydration of cyanohydrins.

for the borate-catalyzed conversion have not been reported in the literature. The rates of hydration achieved using the borate salts are adequate (TOF = 0.25 h^{-1} for ACH at 65 °C at pH 8.9); however, the low yields (70–80%), high catalyst loadings (>20%), and large amount of acetone cosolvent used in the conversion limit their practical utility.

3. Lessons learned from investigations of homogeneous nitrile hydration catalysts

The limitations of the current routes to alkylacrylic monomers, methacrylic monomers in particular, from nitrile substrates are clear. However, poor mechanistic understanding of enzymatic and heterogeneous catalysts has impeded successful implementation of more sustainable catalytic solutions. In contrast, it is worth noting that structural and kinetic analyses of homogeneous, stoichiometric nitrile hydrations have provided a fundamental understanding of solution-state metal–nitrile interactions [7] and, thus, have been pivotal in aiding the rational design of catalytic systems. Based on these studies, it is known that metal ions lower the barrier to nitrile hydration by activating the nitrile substrate, the water or hydroxide nucleophile, or both upon coordination. In addition, the imino ion formed in the transition state can be stabilized by interaction with the metal center, which may reduce the amount of solvent ordering required in the transition state [39]. This assertion is supported by the unusually positive $\Delta S^{\ddagger}$ value (+14 e.u.) reported for external hydroxide attack on a 2-cyano-1,10-phenanthroline-ligated Ni^{2+} complex in water compared with that of the base-catalyzed transformation catalyzed by NaOH in the absence of Ni^{2+} ($\Delta S^{\ddagger} = -20$ e.u.) [39].

These stabilizing factors lead to impressive rate accelerations for the metal-mediated processes. In water, hydroxide adds to nitrile ligands coordinated to Co(III) [40–44], Ni(II) [39], and Cu(II) [39] ammine complexes 10^6–10^9 times faster than the rate of hydration performed in the absence of the metal. Even larger rate enhancements were observed in cases where the hydroxide or water nucleophile was also bonded to the metal center, leading to a higher local concentration of reactants and intramolecular nucleophilic attack. The synergetic effect of nitrile activation and intramolecular nucleophilic attack is demonstrated by the 10^{18}-fold rate increase noted for the Hg^{2+}-catalyzed hydrolysis of the pendant nitrile ligand in *cis*-$[Co(en)_2(NH_2CH_2CN)(OH)_2]^{3+}$ (en = ethylenediamine) [45]. In this example, experiments showed that Hg^{2+} coordination activated the nitrile ligand toward nucleophilic attack of the hydroxo ligand bonded to Co^{3+}. The hydration of the aminoacetonitrile ligand in the absence of Hg^{2+} ($k_{obs} = 1.15 \times 10^{-2}\ s^{-1}$) is 10^7 times slower than the Hg^{2+}-catalyzed reaction ($k_{obs} = 5 \times 10^5\ s^{-1}$). (Although the nitrile is not coordinated, the nitrile carbon is only three atoms away from the Co center and likely experiences inductive effects.) The $\Delta S^{\ddagger}$ measured for the hydration in the absence of catalyst (−31 e.u.) is quite negative, indicating increased geometric constraints in the transition state leading



Scheme 9. Formation of a μ-acetamido-μ-amido-octa-amminedicobalt(III) dimer via intramolecular hydroxide attack on an acetonitrile ligand.

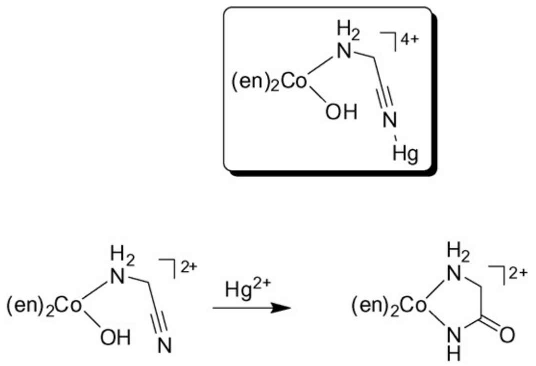


Fig. 1. Binuclear intramolecular hydration of $[(en)_2Co(OH)(NH_2CH_2CN)]^{2+}$ catalyzed by Hg^{2+}.

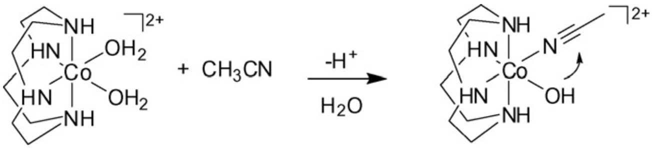
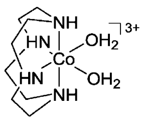


Fig. 2. Substitution of a labile aqua ligand with acetonitrile followed by the intramolecular addition of hydroxide.

to the formation of the five-membered chelated amido product (Fig. 1). In a different example of binuclear activation, Curtis et al. [44] report a 10^{15}-fold rate acceleration in acetonitrile hydration via intramolecular nucleophilic attack in a μ-hydroxo-μ-amido Co dimer following rate determining loss of a nitrile ligand (Scheme 9). Unfortunately, the acetamide product was not released from the coordination sphere. Instead, an inert μ-acetamido-μ-amido Co dimer formed as the final reaction product, even at low pH.

The lability of aqua and hydroxo ligands has also been exploited to promote catalysis by providing a vacant site for coordination of free nitrile substrates. For example, catalysis was first observed at Co^{3+} when Chin et al. investigated $[Co(cyclen)(OH_2)_2]^{3+}$ **1**, $[Co(dmcyclen)(OH_2)_2]^{3+}$ **2**, $[Co(TAEA)(OH_2)_2]^{3+}$ **3**, and $[Co(TAPA)(OH_2)_2]^{3+}$ **4** [46,47].



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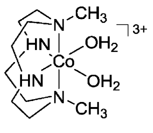

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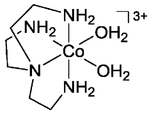

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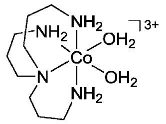

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Complex **1** was the fastest catalyst, with a rate acceleration of about 10^{10} in the hydration of acetonitrile at 40 °C via an intramolelcular addition. In addition, **1** is the only Co complex reported to date that has shown selective acrylonitrile hydration to acrylamide with no byproducts [46]. The aqua ligands of **1** are quite acidic ($pK_{a1} = 5.6$ and $pK_{a2} = 8.0$), and catalysis at neutral pH was proposed to proceed by σ-coordination of the nitrile followed by intramolecular attack of the *cis*-hydroxo nucleophile (Fig. 2) [46,47]. Intramolecular attack yields a four-membered Co metallocycle intermediate that was observed by UV–Vis spectroscopy and ^{13}C NMR spectroscopy. A chelated benzamide was isolated and characterized by X-ray diffraction. Unfortunately, no kinetic data were reported for the acrylonitrile hydration.

Ligand scaffolds that enforce a cis arrangement of aqua ligands have proven useful (see Table 1 entries 1, 54, and 56–58) and have been used as a general design strategy for metal-catalyzed hydrolytic transformations in water [6,48]. In addition, many other ligand designs have provided a number of catalytic systems that collectively show remarkable chemoselectivity, affording amides with little to no acid byproduct. While many of the early nitrile hydration catalysts are plagued by low conversions and limited substrate range, an advanced understanding of the reactivity of nitriles with transition metals has led to the development of elegant catalytic systems that can be used under very mild reaction conditions (i.e. ambient or low temperature, neutral pH), show excellent function group tolerance, and are applicable to mutlicomponent syntheses of complex organic molecules. Furthermore, several homogeneous catalysts have proven effective in regioselective conversions of acrylonitrile and methacrylonitrile. Investigations of distinct, homogeneous nitrile hydration catalysts and NHase mimics may also provide the understanding necessary to enable the innovation of a new class of nitrile hydration catalysts for the manufacture of acrylic monomers. The following paragraphs highlight the contributions of homogeneous nitrile hydration catalysts with an emphasis on the various modes of reactivity influenced by different metals and ligand platforms, as well as the use of acrylonitrile substrates.

3.1. *Overview of homogeneous nitrile hydration catalysis and viable mechanistic pathways*

A list comparing the catalytic activity of homogeneous transition metal complexes in the hydration of acetonitrile to acetamide is summarized in Table 1. (In several cases, acetonitrile hydration was not reported, and the data shown pertain to an alternative substrate. Alternative substrates are noted under the comments column for the respective catalyst. Note that TOF values were not reported for some of the studies. In those cases, the TOF values listed in the table were calculated from the available rate data. Because the TOFs were derived using various methods, the values should only be used to give a crude measure of how the catalysts compare.) Ten of the homogeneous catalysts listed have demonstrated regioselective conversions of unsaturated nitriles yielding amides with retention of the C=C bond (Table 2). Other catalysts listed in Table 1 contribute invaluable data about the diverse ways in which the electronic and geometric structure of the transition metals can be tweaked to afford new reaction pathways and to enhance catalytic activity, selectivity, and functional group compatibility.

3.1.1. *Molybdenum-catalyzed nitrile hydration*

Molybdocene complexes of the type $[Cp^R_2M(OH)(OH_2)]^+$ (where M = Mo or W and $Cp^R = C_5H_5, C_5H_4Me$, or *ansa*-$\{(C_5H_4)_2C_2Me_4\}$) are the only *early* transition metal complexes that have demonstrated catalytic nitrile hydration to date. In fact, these molybdocene complexes show impressive hydrolytic activity [83], promoting the addition of water across C≡N [49,85], C–O [85], P–O [86–88], and P–S [87,89,90] bonds in a variety of molecules containing these functional groups. The hydration of C≡N bonds in nitrile substrates is selective, affording amides without further hydration to the carboxylic acid. The unique hydrolytic activity of the ionic molybdocene complexes is primarily attributed to their unusual resistance to loss of the Cp ligands [83]. In fact, the Cp_2Mo^{2+} core remains intact in anaerobic water for weeks while most early metal metallocenes undergo Cp–M hydrolysis. In addition, $Cp_2Mo(OH_2)^{2+}$ is the least acidic of the bis(aqua)metallocenes ($pK_{a1} = 5.5$ and $pK_{a2} = 8.5$), which conveniently affords the $[Cp^R_2Mo(OH)(OH_2)]^+$ cation as the predominant species at neutral pH. As alluded to above, the *cis* arrangement of the aqua and hydroxo ligands is integral to the observed reactions. However, one drawback of using inner-sphere aqua ligands to facilitate the addition of water to activated organic molecules is the tendency of such metal complexes to form multinuclear μ-hydroxo complexes, such as the dicationic dimer shown in Scheme 10 [91,92]. These equilibrium processes reduce the rate of hydration by changing the catalyst concentra-

Table 1
Summary of selected data available for nitrile hydration catalysts reported to date[a].

	Catalyst	Temperature (°C)	mol% catalyst	TOF[b] (mol/mol catalyst × h)	Comments	Reference
Molybdenum						
1	$[Cp_2Mo(OH)(OH_2)][OTs]$	80	0.5	4.77	Reaction carried out in D_2O buffered at pD 7.2. Only 61% conversion noted, but catalyst was still active. Regioselective acrylonitrile hydration[c] reported, as well as a variety of other nitrile substrates.	[49]
Ruthenium						
2	*cis*-$Ru(acac)_2(PPh_2py)_2$ (**15**)	180	0.024	20,900	Reactivity was not examined for acetonitrile. Reported values are for hydration of benzonitrile. Reaction carried out under argon atmosphere with 1 mmol benzonitrile, 4 mmol water in 0.5 mL DME. 85% conversion noted after 10 min. Hydration of a variety of other nitriles, including cinnamonitrile, was investigated.[c]	[50]
3	$[Ru(H_2O)(NCMe)_4(P\mathit{i}Pr_3)]BF_4$ (**5**)	55	0.01	50	Reaction carried out under argon atmosphere at pH 10.5 using 1:1 acetonitrile:water. 15.2% conversion noted after 120 h.	[51]
4	$[RuCl(\eta^6$-*p*-cymene)(ethyl maltol)]	75	0.17	23.4	Reactivity was not examined for acetonitrile. Reported values are for hydration of trichloroacetonitrile. Reaction carried out under Argon atmosphere in 1:7 nitrile:water. TON 562, 94.2% yield after 24 h noted. 3.1% acetate sideproduct was produced.	[52]
5	*cis*-$Ru(acac)_2(L_2)_2$ L2 = 3-diphenylphosphinoisoquinilone (**17**)	120	1	20	Reactivity was not examined for acetonitrile. Reported values are for hydration of 4-methylbenzonitrile. Reaction carried out under Argon atmosphere with 1 mmol nitrile, 2 mmol water in 1 mL DME. 100% conversion noted after 20 h.	[53]
6	$[RuCl(\eta^6$-*p*-cymene)(methyl maltol)]	75	0.17	17.6	Reactivity was not examined for acetonitrile. Reported values are for hydration of trichloroacetonitrile. Reaction carried out under Argon atmosphere in 1:7 nitrile:water ratio. TON 424, 71.5% yield after 24 h noted. 2.0% acetate sideproduct was produced.	[52]
7	$[RuCl(\eta^6$-*p*-cymene)(Kojic acid)]	75	0.17	17.4	Reactivity was not examined for acetonitrile. Reported values are for hydration of trichloroacetonitrile. Reaction carried out under Argon atmosphere in 1:7 nitrile:water ratio. TON 417, 55.0% yield after 24 h noted. 2.2% acetate sideproduct was produced.	[52]
8	$[RuCl_2(\eta^6$-*p*-cymene)(3,5,6-bicyclophosphite-α-D-glucofuranoside-dimethylhemiketal)]	75	0.17	14.45	Reactivity was not examined for acetonitrile. Reported values are for hydration of trichloroacetonitrile. Reaction carried out under Argon atmosphere in 1:7 nitrile:water ratio. TON 347, 58.0% yield after 24 h noted. 2.1% acetate sideproduct was produced.	[54]
9	$[RuH(\eta^5\text{-}C_9H_7)dppm]$ (**11**)	120	0.1	12.01	Reaction carried out under dry nitrogen atmosphere in 1:1 nitrile:water. TON 865 after 72 h noted.	[55]
10	$[RuCl(\eta^6$-*p*-cymene)(3-hydroxy-2-methyl-4-pyridone)-$(CH_2)_6$-(3-hydroxy-2-methyl-4-pyridone)$(\eta^6$-*p*-cymene)RuCl]	75	0.17	10.9	Reactivity was not examined for acetonitrile. Reported values are for hydration of trichloroacetonitrile. Reaction carried out under Argon atmosphere in 1:7 nitrile:water ratio. TON 262, 43.7% yield after 24 h noted. 3.0% acetate sideproduct was produced.	[52]
11	$[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)^3$, PTA-Bn = 1-benzyl-3,5-diaza-1-azonia-7-phosphaadamantane chloride (**20d**)	100	5	9.9	Reactivity was not examined for acetonitrile. Reported values are for hydration of benzonitrile. Reaction carried out under N_2 atmosphere, using 0.33 M nitrile in water. 99% yield (86% isolated yield) noted. Also tested w/several other nitriles including acrylonitrile.[c]	[56]
12	$[TpRu(PPh_3)(NHCOCH_3)(H_2O)]$ (**24**)	150	0.5	5.3	Reaction carried out under 10 bar argon pressure, using 200:2000:1 nitrile:water:catalyst, with 1,4-dioxane solvent. TON 128 after 24 h. 8.7% yield noted at 120 °C and 0.1 mol% catalyst loading with neat 1:1 acetonitrile:water. Also tested w/several other nitriles including crotononitrile.	[57]
13	*cis*-$Ru(acac)_2(L_1L_2)$ (**18**)	120	1	5	Reactivity was not examined for acetonitrile. Reported values are for hydration of 4-methylbenzonitrile. Reaction carried out under argon atmosphere with 1 mmol nitrile, 2 mmol water in 1 mL DME. 90% conversion noted after 20 h.	[53]
14	$[TpRu(PPh_3)(\kappa_2$-*N*, *O*-NH=CMeN=CMeO) (**26**)	150	0.5	4.9	Reaction carried out under 10 bar argon pressure, using 200:2000:1 nitrile:water:catalyst, with 1,4-dioxane solvent. TON 118 noted after 24 h.	[57]
15	*cis*-$Ru(acac)_2(PBu_3)_2$ (**13**)	180	2	1.85	Reactivity was not examined for acetonitrile. Reported values are for hydration of benzonitrile. Reaction carried out under argon atmosphere with 1 mmol benzonitrile, 2 mmol water in 0.5 mL DME. 89% conversion noted after 24 h.	[58]
16	*cis*-$Ru(acac)_2(PPh_3)_2$ (**14**)	180	2	1.31	Reactivity was not examined for acetonitrile. Reported values are for hydration of benzonitrile. Reaction carried out under argon atmosphere with 1 mmol benzonitrile, 2 mmol water in 0.5 mL DME. 63% conversion noted after 24 h.	[58]
17	$RuH_2(PPh_3)_4$	120	3	1.28	Reaction carried out under argon atmosphere, using 1 mmol nitrile, 2 mmol water, and 0.5 mL DME. 92% conversion noted after 24 h.	[59]

Table 1 (*Continued*)

	Catalyst	Temperature (°C)	mol% catalyst	TOF[b] (mol/mol catalyst × h)	Comments	Reference
18	$RuCl_3 \cdot nH_2O$	76	0.3	0.5	Reaction carried out using 1:300:450 catalyst:nitrile:water. TON 10, 3.4% conversion after 22 h.	[60]
19	$[Ru(CO)_3Cl_2]_2$	76	0.3	0.02	Reaction carried out using 1:300:450 catalyst:nitrile:water. TON 0.5, 0.2% conversion after 22 h.	[60]
20	$[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_2(OEt))]$ (**9a**)	100	5	0.93	Reactivity was not examined for acetonitrile. Reported values are for hydration of benzonitrile. Reaction was carried out using 0.15 M nitrile and 150 mM TritonX100 surfactant in water. 93% conversion after 20 h noted. Hydration of other nitriles was examined, including 2-butenenitrile.[c] This catalyst hydrated the cyanohydrin lactonitrile, with a 14% yield after 24 h.	[61]
21	$[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh(OEt)_2)]$ (**8a**)	100	5	–	Reactivity was not examined for acetonitrile. Reported values are for hydration of benzonitrile. Reaction was carried out using 0.15 M nitrile and 150 mM TritonX100 surfactant in water. 37% conversion after 20 h noted.	[61]
22	$[TpRuH(PPh_3)(CH_3CN)]$ (**23**)	120	0.1	–	Reaction carried out under 10 bar argon pressure, using 1000:1000:1 nitrile:water:catalyst. 8.3% conversion noted at 120 °C and 0.1 mol% catalyst loading.	[57]
23	$\{[(PCy_3)(CO)RuH]_4(\mu_4\text{-}O)(\mu_3\text{-}OH)(\mu_2\text{-}OH)\}$ (**27**)	80–90	1	–	Reactivity was not examined for acetonitrile. Reported values are for hydration of benzonitrile. Reaction carried out under inert atmosphere with 2 mmol nitrile, 40–60 mmol water, and 2–3 mL of 2-propanol. 99% conversion after 8 h was noted. Also tested w/several other nitriles including acrylonitrile.[c]	[62]
24	*cis*-$Ru(acac)_2(PMe_3)_2$ (**12**)	180	2	–	Reactivity was not examined for acetonitrile. Reported values are for hydration of benzonitrile. Reaction carried out under argon atmosphere with 1 mmol benzonitrile, 2 mmol water in 0.5 mL DME. 55% conversion noted after 24 h.	[58]
25	*cis*-$Ru(acac)_2(L_1)_2$L1 = 6-diphenylphosphini-N-pivaloyl-2-aminopyridine (**16**)	120	1	–	Reactivity was not examined for acetonitrile. Reported values are for hydration of 4-methylbenzonitrile. Reaction carried out under Argon atmosphere with 1 mmol nitrile, 2 mmol water in 1 mL DME <5% conversion noted after 20 h.	[53]
Osmium						
26	$[OsCl_2(Hbzim)(dmso)_3]$, Hbzim = benzimidazole	75	0.13	17	Reported values are for trichloronitrile. Acetonitrile is unreactive. Reactions carried out in Ar atmosphere in1:7 chloronitrile:water. 82.7% conversion after 24 h.	[63]
27	$[OsCl_2(\eta^6\text{-}p\text{-cymene})(PPh(OEt)_2)]$	100	5	0.83	Reactivity was not examined for acetonitrile. Reported values are for hydration of benzonitrile. Reactivity was examined in water using 150 mM TritonX100 surfactant. 82% conversion after 20 h.	[61]
28	$[OsCl(\eta^6\text{-}p\text{-cymene})$(3-hydroxy-2-methyl-4-pyridone)-$(CH_2)_6$-(3-hydroxy-2-methyl-4-pyridone)$(\eta^6\text{-}p\text{-cymene})OsCl]$	75	0.17	8	Reactivity was not examined for acetonitrile. Reported values are for hydration of trichloroacetonitrile. Reaction carried out under Argon atmosphere in 1:7 nitrile:water ratio. TON 192, 35.2% yield after 24 h noted. 0.8% acetate sideproduct was produced.	[52]
29	$[Os(CO)_3Cl_2]_2$	76	0.3	4.6	Reaction carried out using 1:300:450 catalyst:nitrile:water. TON 102, 34% conversion after 22 h.	[64]
30	$OsCl_3 \cdot nH_2O$	76	0.3	0.6	Reaction carried out using 1:300:450 catalyst:nitrile:water. TON 13, 4.3% conversion after 22 h.	[64]
Cobalt						
31	$[Co(cyclen)(OH_2)_2]^{3+}$, cyclen = 1,4,7,11-tetraazacyclododecane (**1**)	40	2–10	12	Reaction carried out at pD 7 using 0.1 M acetonitrile in D_2O. TON 10, 100% conversion noted. Also tested w/several other nitriles including acrylonitrile.[c]	[46,47]
32	$[Co(TAEA)(OH_2)_2]^{3+}$, TAEA = tris(2-aminoethyl)amine (**3**)	40	2–10	0.6	Reaction carried out at pD 7 using 0.1 M acetonitrile in D_2O, 100% conversion noted.	[46]
33	$[Co(PyPS(SO_2))(OH)]^{2+}$ (**29**)	40	0.14	24	Reaction carried out under inert atmosphere using 0.04 mmol catalyst in 3.5 mL Tris buffer (pH 8) and 1.5 mL acetonitrile, TON 18 noted. Hydration was only examined for acetonitrile.	[65]
34	$[Co(PyPS)(OH)]^{2+}$ (**28**)	40	0.14	8	Reaction carried out under inert atmosphere using 0.04 mmol catalyst in 3.5 mL Tris buffer (pH 8) and 1.5 mL acetonitrile. Hydration was only examined for acetonitrile.	[65]
35	$[Na[Co(L\text{-}N_2SOSO)(tBuNC)_2]$ (**30**)	4	8.3	–	Reaction carried out under inert atmosphere using 0.5 mL acetonitrile and 0.5 mL HOAc/NaOAc buffer (1 M, pH 4.8). TON 18, 4.2% conversion noted after 17 h, TON 50 after 6 days. Hydration was only examined for acetonitrile.	[66]
Rhodium						
36	$[Rh(COD)Cl]_2$/TPPTS/NaOH	90	0.005	295.3	Carried out in degassed water at pH 11.7 under 80 psi N_2 in an autoclave. TON of 934 reported. Acrylonitrile was not tested. Reaction carried out in absence of base (pH 7) yielded amide at rate of 50.8 h^{-1}.	[67]
37	$[Rh(COD)Cl]_2$/TPPTS/NaOH	80	0.005	207	Carried out in degassed water at pH 11.7 under 80 psi N_2 in an autoclave. Hydration was only demonstrated for acetonitrile.	[67]

Table 1 (*Continued*)

	Catalyst	Temperature (°C)	mol% catalyst	TOF[b] (mol/mol catalyst × h)	Comments	Reference
38	$[Rh(COD)Cl]_2$	80	0.005	68.5	Carried out in degassed water at pH 11.7 under 80 psi N_2 in an autoclave. Hydration was only demonstrated for acetonitrile.	[67]
39	$[Rh(COD)Cl]_2/PPh_3$	80	0.005	60.5	Carried out in degassed water at pH 11.7 under 80 psi N_2 in an autoclave. Hydration was only demonstrated for acetonitrile.	[67]
40	*trans*-$Rh(OH)(CO)(Ph_3)_2$	80	0.1	50	Heated at reflux with water cosolvent for 3 h, also tested w/several other nitriles including acrylonitrile.[c]	[68]
41	$[Rh(COD)Cl]_2$/TPPTS/NaOH	25	0.005	31	Carried out in degassed water at pH 11.7 under 80 psi N_2 in an autoclave.	[67]
42	$Rh(COD)(OMe)/PCy_3$	25	0.5	8.3	Data given for propionitrile substrate. Successful hydrations of several other aliphatic, unsaturated, and aromatic nitriles were reported, in addition to the dintrile $CN(CH_2)_4CN$. Bulky nitriles required the addition of base, Na_2CO_3 or NaOH for complete conversion. Methacrylonitrile was regioselectively converted to methacrylamide, but acrylonitrile was not tested.	[69]
43	$RhCl(PPh_3)_3$	Reflux	0.025	0.19	Water used as a cosolvent, acrylonitrile was hydrated selectively.[c]	[70]
Iridium						
44	IrH(CO)TPPTS	100	1.7	5.7	Reactions carried out in water for 4 h under N_2, 38% yield reported. Methacrylonitrile and several other unsaturated nitriles were hydrated regoselectively to unsaturated amides, but acrylonitrile could not be hydrated.	[71]
45	$[Ir(O_2)(PMe_3)_4]Cl$	140	0.1	4.1	Carried out in 1:1 (v/v) $MeCN/H_2O$ sealed tube. 82% yield and TON 846 noted. Hydration was only demonstrated for acetonitrile.	[72]
46	*trans*-$Ir(OH)(CO)(Ph_3)_2$	80	0.1	1.25	Refluxed in 2:5 (v/v) water:nitrile solution for 20 h. Hydration was only demonstrated for acetonitrile.	[68]
Nickel						
47	$[(dippe)Ni(\eta^2\text{-}NCCH_3)]$	180	0.04	4	Hydration was conducted under 100psi argon pressure at pH 7 with 4:1 nitrile:water. TON 257, 10% conversion noted.	[60]
48	$[(dippe)Ni(\eta^2\text{-}NCPh)]$	180	0.04	14	Hydration was only examined for benzonitrile. Reaction carried out at pH 7 with 4:1 nitrile:water. TON 984, 41% conversion noted.	[60]
49	$[(dtbpe)Ni(\eta^2\text{-}NCPh)]$	180	0.04	9	Hydration was only examined for benzonitrile. Reaction carried out at pH 7 with 4:1 nitrile:water. TON 651, 23% conversion noted.	[60]
50	$[(dcype)Ni(\eta^2\text{-}NCPh)]$	180	0.04	6	Hydration was only examined for benzonitrile. Reaction carried out at pH 7 with 4:1 nitrile:water. TON 467, 17% conversion noted.	[60]
Palladium						
51	$LPd_2(NHCOMe)$ (**31**)	76	–	80	Acidic MeCN:Water:THF solvent mixture (5:2:1 v/v), TOF value taken from graph in reference Fig. 1 at $[HBF]/[LPd_2(NHCOMe)]$ ~20. >4000 turnovers reported. Hydration of acrylonitrile was selective.	[73]
52	$[Pd(OH_2)_4][ClO_4]_2$	40	10	52.2	Reaction performed 0.02 M D_2O in $CD_3C(O)$ and adjusted to pD 2–3 using $DClO_4$. $CHCl_2CN$ substrate (0.17 M) was used due to slow rate of MeCN hydration. 1000 turnovers were noted.	[74]
53	$PdCl(OH)(bipy)(H_2O)$	76	0.3	29.4	Performed in 6:1 water:nitrile (mole ratio) solution at pH 5.5, TOF calculated from % conversion (67.5%) at 3 h.	[75]
54	*cis*-$[Pd(Met\text{-}OMe)(OH_2)_2][ClO_4]_2$	40	10	10.5	Reaction performed 0.02 M D_2O in $CD_3C(O)$ and adjusted to pD 2–3 using $DClO_4$. $CHCl_2CN$ substrate (0.17 M) was used due to slow rate of MeCN hydration.	[74]
55	K_2PdCl_4, 2,2-bipy, NaOH	76	0.5	8.8	3:1 water:nitrile solution (mole ratio), pH 10.4, TOF calculated from % conversion at 5 h, 56% amide and 0.7% acetic acid observed at 48 h.	[75,76]
56	*cis*-$[Pd(en)(OH_2)_2][ClO_4]_2$	40	10	3.9	Reaction performed 0.02 M D_2O in $CD_3C(O)$ and adjusted to pD 2–3 using $DClO_4$. $CHCl_2CN$ substrate (0.17 M) was used due to slow rate of MeCN hydration.	[74]
57	*cis*-$[Pd(dtod)(OH_2)_2][ClO_4]_2$	40	10	1.64	$CHCl_2CN$ used instead of MeCN. Reaction performed in D_2O in $CD_3C(O)$ using 0.17 M nitrile and adjusted to pD 2–3 using $DClO_4$.	[77]
58	*cis*-$[Pd(dtcol)(OH_2)_2][ClO_4]_2$	40	10	0.5	Reaction performed 0.02 M D_2O in $CD_3C(O)$ and adjusted to pD 2–3 using $DClO_4$. $CHCl_2CN$ substrate (0.17 M) was used due to slow rate of MeCN hydration.	[74]
59	$[Pd(dien)(OH_2)][ClO_4]$	40	10	0.2	Reaction performed 0.02 M D_2O in $CD_3C(O)$ and adjusted to PD 2–3 using $DClO_4$. $CHCl_2CN$ substrate (0.17 M) was used due to slow rate of MeCN hydration.	[74]
Platinum						
60	$[PtH(PMe_2OH)(PMe_2O)_2H$ (**34**)	90	0.02	380	Reaction was refluxed in 1:1.5 mol nitrile:water. 5700 turnovers observed, and 77% yield of isolated acetamide. Successful hydration of a variety of substituted nitriles was reported, including the regioselective hydration of acrylonitrile.[c]	[78]

Table 1 (*Continued*)

	Catalyst	Temperature (°C)	mol% catalyst	TOF[b] (mol/mol catalyst × h)	Comments	Reference
61	*trans*-[$PtH(H_2O)(PMe_3)_2$][OH]	78	0.2	178.4	1 equiv. of NaOH and PtCl starting material were used. reaction mixtures were sealed under vacuum and heated in aqueous solution (1:1 vol. water:nitrile). 5000–6000 turnovers observed. Catalyst hydrated C=C bond in acrylonitrile preferentially.[c]	[79]
62	*trans*-[$PtH(H_2O)(PEt_3)_2$][OH]	78	0.2	69.9	1 equiv. of NaOH and PtCl starting material were used. reaction mixtures were sealed under vacuum and heated in aqueous solution (1:1 vol. water:nitrile).	[79]
63	*trans*-[$Pt(CH_3)(NHCOCH_3)(PPh_3)_2$]	80	0.1	30	Heated at reflux with water cosolvent for 2.5 h.	[68]
64	Pt[P(*c*-C_6H_{11})$_3$]$_2$	80	0.03–0.1	26	Water cosolvent (17% by volume), 520 turnovers in 20 h reaction, hydrates C=C bond of acrylonitrile preferentially.[c]	[80]
65	*trans*-[$PtH(H_2O)(PMe_3)_2$][OH]	25	0.2	21.5	1 equiv. of NaOH and PtCl starting material were used. Reaction was performed under N_2 in aqueous solution (1:1 vol. water:nitrile). Acrylonitrile hydration becomes selective for CN bond at lower temp, but byproducts were still observed.[c]	[79]
66	Pt(P(*i*-Pr_3)$_3$	80	0.03–0.1	20.3	Water cosolvent (17% by volume), 405 turnovers in 20 h reaction, hydrates C=C bond of acrylonitrile preferentially.[c]	[80]
67	$Pt(OH)Ph(PEt_3)_2$	80	0.06	8.7	Heated in aqueous solution (1:1 mol water:nitrile) for 20 h under N_2, hydration of acrylonitrile gave a mixture of products.	[81]
68	$Pt(C_6H_9)(OH)$(diphos)	80	0.1	6.8	Heated at reflux with water cosolvent for 1 h.	[68]
69	Pt(OH)Ph(P-*t*-$BuMe_2$)$_2$	80	0.06	6.45	Heated in aqueous solution (1:1 mol water:nitrile) for 20 h under N_2, hydration of acrylonitrile gave a mixture of products.	[81]
70	$Pt(C_6H_8)$(diphos)	80	0.1	5.7	Heated at reflux with water cosolvent for 3 h, catalyst is converted to Pt-amido complex.	[68]
71	*trans*-$Pt(NHCOMe)Ph(PPh_3)_2$	80	0.06	5.1	Heated in aqueous solution (1:1 mol water:nitrile) for 20 h under N_2. hydration of acrylonitrile gave a mixture of products.	[81]
72	Pt(PPh(*t*-Bu)$_2$)$_2$	80	0.03–0.1	4.95	Water cosolvent (17% by volume), 20 h reaction, TON = 99. Hydrates C=C bond of acrylonitrile preferentially.[c]	[80]
73	*trans*-$Pt(OH)Ph(PPh_3)_2$	80	0.03–0.1	3.85	Water cosolvent (17% by volume), 20 h reaction hydrates C=N bond of acrylonitrile preferentially, but byproducts are observed.[c]	[80]
74	$Pt(C_6H_8)(PPh_3)_2$	80	0.1	3.62	Heated at reflux with water cosolvent catalyst (16 h) is converted to $Pt(C_6H_9)(NHC(O)CH_3)(PPh_3)_2$, which catalyzed hydration at a faster rate (TOF = 7 h^{-1}) when used as the starting material.	[68]
75	Pt(OH)Me(P-*t*-Bu_2Me)$_2$	80	0.06	3.15	Heated in aqueous solution (1:1 mol water:nitrile) for 20 h under N_2, hydration of acrylonitrile gave a mixture of products.	[81]
76	$Pt(PEt_3)_3$	80	0.03–0.1	2.7	Water cosolvent (17% by volume), 20 h reaction, TON = 54. Hydrates C=C bond of acrylonitrile preferentially.[c]	[80]
77	Pt(OH)Ph(P-*t*-Bu_2Me)$_2$	80	0.06	1.1	Heated in aqueous solution (1:1 mol water:nitrile) for 20 h under N_2, hydration of acrylonitrile gave a mixture of products.	[81]
78	*trans*-$Pt(OH)(CCl{=}CCl_2)(PPh_3)_2$	80	0.03–0.1	0.9	Water cosolvent (17% by volume), 20 h reaction hydrates C=N bond of acrylonitrile preferentially, but byproducts are observed.[c]	[80]
79	*trans*-$Pt(OH)(CH{=}CCl_2)(PPh_3)_2$	80	0.03–0.1	0.75	Water cosolvent (17% by volume), 20 h reaction hydrates C=N bond of acrylonitrile preferentially, but byproducts are observed.[c]	[80]
Gold						
80	(IPr)Au(NTf_2)	140	2	25	Reactions carried out in a sealed vial at 7 bar with a 1:1 water:THF (v/v) solvent mixture for 2 h in a microwave. Hydration was also demonstrated using a variety of substituted benzonitriles, heteroaromatic, and aliphatic nitriles. Fumaronitrile was hydrated to unsatuated monoamide, but acrylonitrile was not tested.	[82]
Zinc						
81	$Zn(NO_3)_2{\cdot}6H_2O$/2-propanone oxime	0.66	10	7.7	Used 1:2 molar ratio of Zn:ketoxime in aqueous nitrile solution (1:2 nitrile:water). Observed 47% yield acetamide after 10 h reflux with rigorous stirring. A variety of nitriles were tested giving biphasic mixtures due to immiscibility with water. TOF up to 37 h $^{-1}$ and TON up to 1000 were observed.	[119]
82	NaOH	78		0.4		[79]

[a] Data shown are for the hydration acetonitrile unless otherwise stated. See comments written for each catalysts.

[b] TOFs were calculated from available rate data in cases when it was not reported directly. As a result, some are initial TOFs while others are average TOFs.

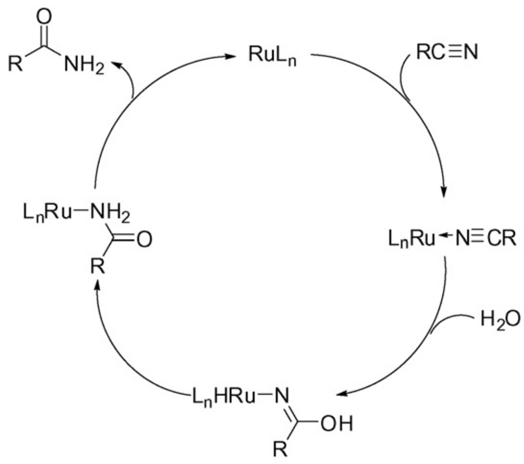
[c] See Table 2 for acrylonitrile hydration conditions.

tion, and they complicate kinetic analyses of the catalytic reactions. As a result, some understanding of the speciation is vital for interpretation of the observed reactivity.

The aqua ligand of $Cp_2Mo(OH)(OH_2)^+$ is labile, and its dissociation provides a vacant site for the coordination of substrates. The metal-bound hydroxo ligand is quite nucleophilic and reacts with the coordinated substrate to yield a four-membered metallocycle, which is a precedented structural motif in molybdocene chemistry [93]. The intramolecular mechanism is supported by two observations. First, the optimal reaction pH (pH 6–7) is within the range of the pK_a values measured for the aqua ligands, and second, the reaction rates decrease significantly at low and high pH [85,86]. With regard to this latter observation, at low pH, the hydroxo ligand is protonated to a less nucleophilic aqua ligand, which will decrease the rate. Under basic conditions, the neutral bis(hydroxo) $Cp_2Mo(OH)_2$ species predominates, and the Mo–OH bonds are relatively inert to substitution by the organic substrates, leading to a drastic decrease in rate above pH 8.

Substrate and product inhibition in the $Cp_2Mo(OH)(OH_2)^+$ system led to complicated reaction kinetics and precluded the determination of activation parameters for the nitrile hydration [49]. However, the activation parameters measured for the related $Cp'_2Mo(OH)(OH_2)^+$-catalyzed hydrolysis of ethyl acetate ($Cp' = C_5H_4Me$, $\Delta H^\ddagger = 5.9$ kcal/mol, $\Delta S^\ddagger = -48$ e.u.) [94] and $Cp_2Mo(OH)(OH_2)^+$-catalyzed *p*-nitrophenol phosphate ($\Delta S^\ddagger = -16$ e.u.) [86] are consistent with a constrained transition state, which implicates intramolecular attack as the rate-determining step. Furthermore, a positive Hammett plot was observed for the hydration, indicating the rate enhancing effect of e^- withdrawing nitrile substituents, also consistent with the proposed mechanism. Finally, altering the electronic environment of the Mo^{4+} center by changing the substituents on the Cp rings had no significant effect on the reaction rates, which was attributed to the fact that electronic tuning of the metal center has opposite effects on the bound electrophile and nucleophile [95].

The $Cp_2Mo(OH)(OH_2)^+$ catalyst enabled regioselective conversion of acrylonitrile to acrylamide (with retention of the C=C bond) at an initial rate of 1.35 mol acrylamide/(mol catalyst × h) with 61.8 turnovers (83% conversion). However, cyanohydrin substrates could not be hydrated despite the rapid conversion observed for β-hydroxynitriles (vide infra) [96]. Molybdocene catalysts were also intolerant to ether- and ester-containing nitriles due to facile hydrolysis of those groups [85].

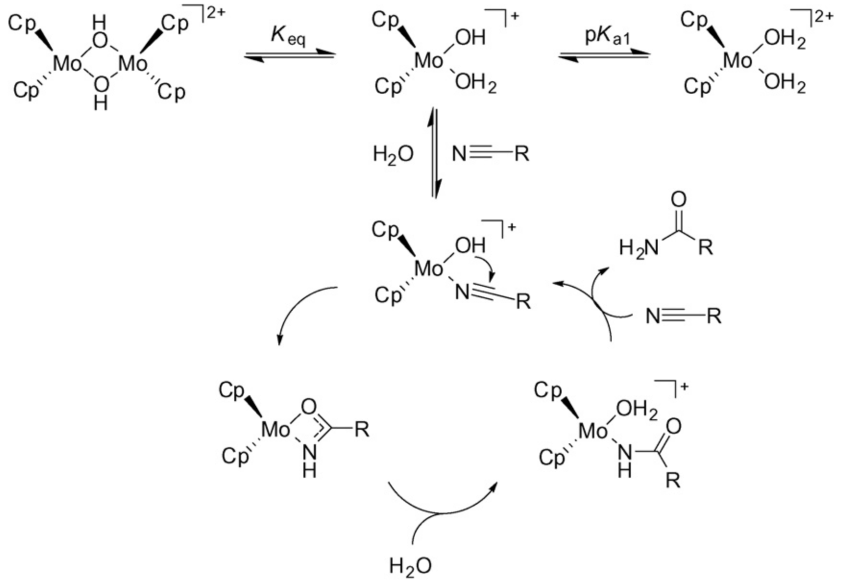


Scheme 11. Cycle proposed for $RuH_2(PPh_3)_4$-catalyzed nitrile hydration.

3.1.2. *Iron, ruthenium, osmium*

Ironically, there are no published examples of catalytic nitrile hydration using homogeneous Fe, even though many nitrile hydratase mimics employ Fe^{3+}. There are, however, several noteworthy examples of stoichiometric nitrile hydration using Fe^{3+}, and more recently Fe^{2+} [97]. Complexes of Ru^{2+}, on the other hand, are some of the most versatile nitrile hydration catalysts discovered to date with regard to substrate tolerance and modes of reactivity, although many of these systems are new and have yet to be extended to unsaturated substrates.

3.1.2.1. Ru as a Lewis acid. Among the first Ru nitrile hydration catalysts reported was the complex developed by Murahashi et al., $[RuH_2(PPh_3)_4]$, [59,98–100]. This complex is capable of hydrating a wide variety of nitriles. The mechanism of hydration involves nucleophilic attack of water on a bound nitrile to give the iminol complex (Scheme 11). Isomerization to the amide and subsequent dissociation regenerates the original Ru complex. An alternative mechanism, in which water is oxidatively added to the ruthe-



Scheme 10. Proposed mechanism for $Cp_2Mo(OH)(OH_2)^+$-catalyzed nitrile hydration and aqueous equilibrium processes that affect catalyst concentration.

Table 2
Summary of selected data available for acrylonitrile hydration catalysts reported to date[a].

	Catalyst	Temperature (°C)	mol% catalyst	TOF (mol/mol catalyst × h)	Comments	Reference
1	$[Cp_2Mo(OH)(OH_2)][OTs]$	80	0.5	1.35	Reaction carried out in D_2O buffered at pD 7.2. 83% conversion noted. No C═C bond hydration detected.	[83]
2	$[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]^{3+}$, PTA-Bn = 1-benzyl-3,5-diaza-1-azonia-7-phosphaadamantane chloride (**20d**)	100	5	3.8	Reaction carried out under N_2 atmosphere, using 0.33 M acrylonitrile in water. 96% yield (77% isolated yield) noted.	[56]
3	$\{[(PCy_3)(CO)RuH]_4(\mu_4\text{-}O)(\mu_3\text{-}OH)(\mu_2\text{-}OH)\}$ (**27**)	80–90	1	–	Reaction carried out under inert atmosphere with 2 mmol nitrile, 40–60 mmol water, and 2–3 mL of DME. 98% conversion after 6 h noted.	[62]
4	$[Co(cyclen)(OH_2)_2]^{3+}$, cyclen = 1,4,7,11-tetraazacyclododecane (**1**)	40	10	–	Reaction carried out at pD 6.3. Reported to be selective, but no values given.	[46]
5	*trans*-Rh(OH)(CO)(Ph$_3$)$_2$	80	0.1	–	Heated at reflux with water cosolvent for 3 h. Good selectivity was noted, but no numbers were given.	[68]
6	$RhCl(PPh_3)_3$	Reflux	0.025	0.50	Water used as a cosolvent, only trace amounts of acrylic acid observed in some cases.	[70]
7	LPd$_2$(NHCOMe) (**31**)	76	–	80	Acidic MeCN:Water:THF solvent mixture (5:2:1 v/v), no byproducts observed by GC.	[73]
8	$PdCl(OH)(bipy)(H_2O)$	76	0.3	–	Performed in 6:1 water:nitrile (mole ratio) solution at pH 5.5.	[84]
9	[PtH(PMe$_2$OH)(PMe$_2$O)$_2$H (**34**)	90	0.02	–	Reaction was refluxed in 1:1.5 (mol) nitrile:water. Only acrylamide was observed.	[78]
10	*trans*-[PtH(H$_2$O)(PMe$_3$)$_2$][OH]	78	0.2	–	1 equiv. of NaOH and PtCl starting material were used. olefin/CN = 2.4.	[79]
11	Pt[P(*c*-C$_6$H$_{11}$)$_3$]$_2$	80	0.03–0.1	–	Water cosolvent (17% by volume), olefin/CN = 10.	[80]
12	*trans*-[PtH(H$_2$O)(PMe$_3$)$_2$][OH]	25	0.2	–	1 equiv. of NaOH and PtCl starting material were used. Reaction was performed under N_2 in aqueous solution (1:1 vol. water:nitrile). olefin/CN = 0.033.	[79]
13	Pt(P(*i*-Pr$_3$)$_3$	80	0.03–0.1	–	Water cosolvent (17% by volume), olefin/CN = 13.	[80]
14	Pt(NHCHMe)Ph(PEt$_3$)$_2$	80	0.06	–	Heated in aqueous solution (1:1 mol water:nitrile) for 20 h under N_2, olefin/CN = 0.41.	[81]
15	Pt(OH)Ph(P-*t*-Bu$_2$Me)$_2$	80	0.06	–	Heated in aqueous solution (1:1 mol water:nitrile) for 20 h under N_2, olefin/CN = 3.4.	[81]
16	*trans*-Pt(NHCOMe)Ph(PPh$_3$)$_2$	80	0.06	–	Heated in aqueous solution (1:1 mol water:nitrile) for 20 h under N_2, olefin/CN = 0.54.	[81]
17	Pt(PPh(*t*-Bu)$_2$)$_2$	80	0.03–0.1	–	Water cosolvent (17% by volume), 20 h reaction, hydrates C═C bond of acrylonitrile preferentially, olefin/CN = 33.0.	[80]
18	*trans*-Pt(OH)Ph(PPh$_3$)$_2$	80	0.03–0.1	–	Water cosolvent (17% by volume), 20 h reaction hydrates C═N bond of acrylonitrile preferentially, olefin/CN = 0.20.	[80]
19	$Pt(PEt_3)_3$	80	0.03–0.1	–	Water cosolvent (17% by volume), 20 h reaction, olefin/CN = 12.6.	[80]
20	*trans*-Pt(OH)(CCl═CCl$_2$)(PPh$_3$)$_2$	80	0.03–0.1	–	Water cosolvent (17% by volume), olefin/CN = 0.12.	[80]
21	*trans*-Pt(OH)(CH═CCl$_2$)(PPh$_3$)$_2$	80	0.03–0.1	–	Water cosolvent (17% by volume), olefin/CN = 0.20.	[80]

[a] TOFs were calculated from available rate data in cases when it was not reported directly. As a result, some are initial TOFs while others are average TOFs.

nium, was discounted when the substitution of the PPh_3 ligands by electron-donating phosphine ligands such as PBu_3, dppe, and dppp failed to accelerate the rate of hydration [99]. When the nitrile hydration reaction was carried out in the presence of alcohols, the corresponding ester was formed. It was proposed that the Ru complex catalyzed the formation of the imidate, and subsequent hydrolysis with water resulted in the formation of the ester and ammonia. When δ-keto nitriles were used as the substrates, ene-lactams were formed via Ru-promoted cyclization [59,98]. See Refs. [99,100] for a more extensive discussion of the reactivity of the $RuH_2(PPh_3)_4$ catalyst with nitriles.

In other work, Joó and co-workers investigated a series of ionic ruthenium complexes with the general structure [RuX(NCMe)$_4$(P*i*Pr$_3$)]BF$_4$ **5** (X = Cl, P*i*Pr$_3$, P(OMe)$_3$, Hpz, MeOH,

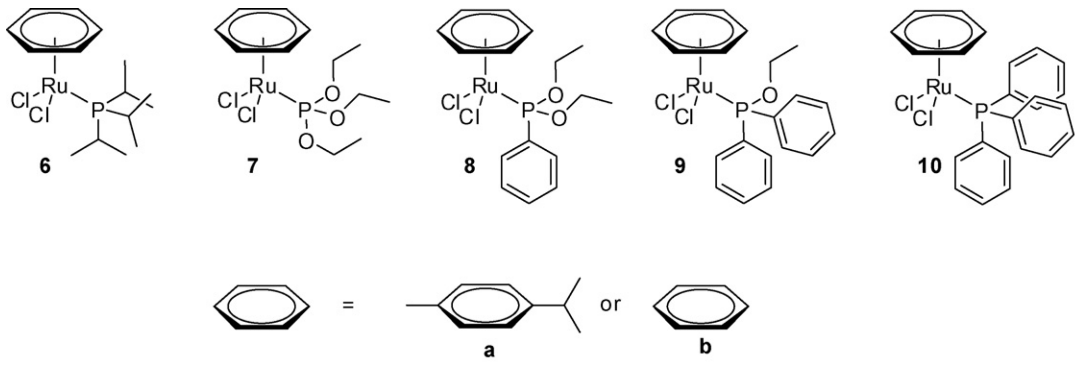
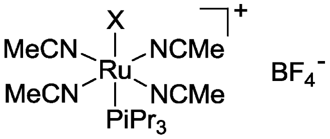


Fig. 3. Ru(II) nitrile hydration catalysts used in water with surfactants.



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H_2O, and OH^-) in aqueous solution [51]. The complex $[Ru(H_2O)(NCMe)_4(PiPr_3)]BF_4$ is formed from $[RuCl(NCMe)_4(PiPr_3)]BF_4$ upon substitution of the Cl ligand by H_2O in aqueous solutions. $[Ru(H_2O)(NCMe)_4(PiPr_3)]BF_4$ is acidic ($pK_a^{H_2O} = 10.5$ at 298 K) and can be deprotonated at pH >9 to the complex $[Ru(OH)(NCMe)_4(PiPr_3)]BF_4$. When $[Ru(OH)(NCMe)_4(PiPr_3)]BF_4$ was dissolved in a dichloromethane solution, it gradually converted to $[Ru(\kappa_2\text{-}NH(CO)CH_3)(NCMe)_3(PiPr_3)]BF_4$. This conversion was proposed to be a part of the catalytic cycle, where an intramolecular nucleophillic attack of the hydroxide on one of the nitrile ligands produced the bidentate acetamide ligand. When an acetonitrile/water mixture was added at 0.01 mol% catalyst loading and 55 °C, acetamide was produced with an initial TOF of $50\,h^{-1}$. Although the catalyst is capable of hydration under mild conditions, it was only active in basic solutions, indicating that the aqua ligand is only sufficiently nucleophilic when deprotonated. Overall, the $[Ru(H_2O)(NCMe)_4(PiPr_3)]BF_4$ complex is promising. It is capable of hydrating acetonitrile at relatively low temperatures and with a TOF that is faster than many other catalysts that operate only at temperatures above 100 °C. More substrate studies are needed to determine the general applicability of this nitrile hydration catalyst.

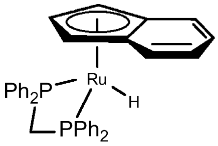
More recently, Cavarzan et al. investigated the catalytic activity of $[RuCl_2(\eta^6\text{-arene})(PR_3)]$ complexes in aqueous solutions, with an emphasis on using surfactants to increase the solubility of these poorly soluble molecules [61]. The complexes investigated are shown in Fig. 3. Aqueous solutions of nitriles were hydrated to amides using 2–5 mol % catalysts and 150 mM concentrations of the surfactant at 100 °C.

The $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_2(OEt))]$ complex (**9a**) was the fastest benzonitrile hydration catalyst, with a TOF = $0.93\,h^{-1}$. Other nitriles were also hydrated by this catalyst, with the intriguing result that nitriles with more electron-withdrawing substituents were hydrated more slowly. It was hypothesized that such nitriles were more hydrophilic and were therefore less likely to interact with the hydrophobic environment contained within the micelle where the catalyst resides. Complex **9a** was also investigated for the hydration of crotonitrile; it hydrated a mixture of E- and Z-isomers to 72% yield after 24 h at 100 °C. The cyanohydrin lactonitrile was also hydrated, and it gave a yield of only 14% after 24 h. When no surfactant was used, the yield decreased only slightly to 10%, which may be a result of decreased catalyst solubility. There was no mention of possible catalyst poisoning, although cyanohydrins are known to degrade at high temperatures in aqueous solutions (vide infra).

The catalytic hydration reactivity of the osmium complex $[OsCl_2(\eta^6\text{-}p\text{-cymene})(PPh(OEt)_2)]$ was also investigated. This molecule hydrated benzonitrile with a TOF of $0.83\,h^{-1}$. This TOF is higher than with the analogous Ru complex **8a** (TOF = $0.37\,h^{-1}$), but the Os complex has not been investigated further.

3.1.2.2. Ligand-assisted activation of H_2O via hydrogen bonding.

The $[RuH(\eta^5\text{-}C_9H_7)dppm]$ complex, **11**, is a part of an interesting class of catalysts that activate water through an outer sphere mechanism. The complex contains a metal–hydride bond that is capable of hydrogen bonding to proton donors (M–H···H–X, M = B, transition metal; X = O, N) and was originally developed to investigate C–H bond activation [55]. When benzonitrile was used as the substrate, hydration to the amide occurred, rather than the expected H–D exchange of the aryl C–H bonds. In fact, benzonitrile was hydrated quickly at 120 °C, yielding 800 turnovers with a 0.1 mol% catalyst loading and a TOF of $11.11\,h^{-1}$.



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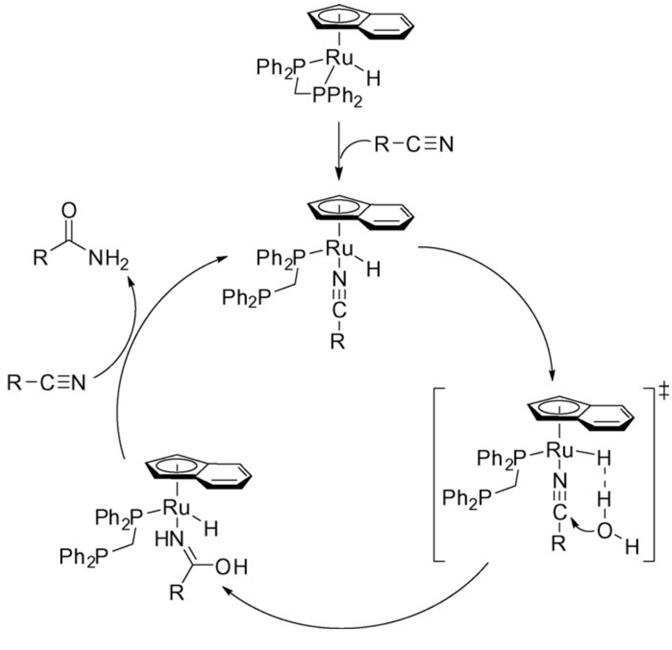
The mechanism of hydration was initially proposed to occur by either of two mechanisms: either by an η^5 to η^3 ring slippage of the indenyl ligand to open a coordination site for the nitrile or by a partial dissociation of the bidentate bis(diphenylphosphine)methane ligand. DFT calculations suggested the second method as most likely. It was proposed that, once the nitrile coordinated to the Ru, nucleophillic attack by water (which is hydrogen bonded to the metal–hydride) produces the α-hydroxyimine, which quickly tautomerizes to the amide upon dissociation (Scheme 12).

The rate-determining step of the reaction was proposed to be the hydrogen-bond-assisted nucleophillic attack of the water on the carbon of the nitrile. This hypothesis was supported by the fact that nitrile hydration did not occur when the related $[RuCl(\eta^5\text{-}C_9H_7)dppm]$ complex was used. DFT calculations also confirmed that the rate-determining step of the reaction is the nucleophillic attack of the water on the nitrile and that the energy of the transition state was lower for the hydride complex than for the chloro complex. A control study with water confirmed that σ-bond metathesis between the Ru–H and H–OH did not occur to give the metal–hydroxide complex, because the $[RuH(\eta^5\text{-}C_9H_7)dppm]$ complex was unchanged in aqueous solution after heating at 80 °C for 4 days.

Oshiki et al. [50] developed a series of $cis\text{-}Ru(acac)_2(PR_3)_2$ complexes, where PR_3 is either PMe_3, PBu_3, PPh_3, or PPh_2py (**12**–**15**) [58]. Of these complexes, **15** was the most reactive toward nitriles, and it was prepared by reaction of $cis\text{-}Ru(acac)_2(\eta^2\text{-}C_8H_{11})_2$ or $cis\text{-}Ru(acac)_2(isoprene)$ with 2 equiv. of PPh_2py.



Scheme 12. Dihydrogen bond-promoted hydration of nitriles using complex **11**.

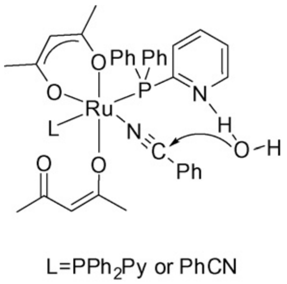


Fig. 4. Pyridine-assisted activation of water by complex **15**.

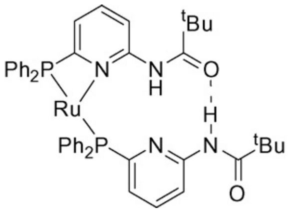
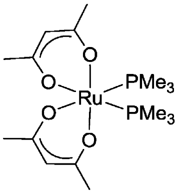


Fig. 5. Potential H-bonding between *P*,*N*-bonded 6-diphenylphosphini-*N*-pivaloyl-2-aminopyridine and 3-diphenylphosphinoisoquinilone.



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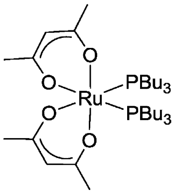

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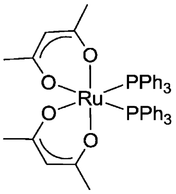

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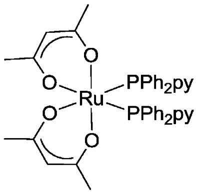

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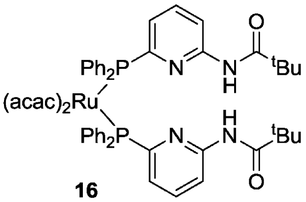
The catalytic hydration of these complexes was examined using benzonitrile as a substrate with a 2:1 water:nitrile ratio at 180 °C in 1,2-dimethoxyethane. Complexes **12**, **13**, and **14** gave only mediocre results under these conditions, with a maximum TOF of 1.85 h^{-1}. However, **15** exhibited extraordinary reactivity, with a TOF of 20,900 h^{-1}. By comparison, **14** had a TOF of only 1.31 h^{-1} under the same conditions. The remarkable reactivity was attributed to a possible intermolecular activation of water by the pyridine nitrogen, as has been observed for the catalytic hydration of alkynes [101]. Although **15** displayed exceptional reactivity, it only displayed this reactivity at high temperatures. Decreasing the temperature to 150 °C decreased the TOF to 222 h^{-1}. Further decreasing the temperature to 80 °C completely halted activity.

In order to investigate the mechanism of hydration, *cis*-Ru(acac)$_2$(PPh$_2$py)(PhCN) was synthesized. No hydration was observed when the stoichiometric conversion of the benzonitrile ligand to benzamide was attempted with excess water in 1,2-dimethoxyethane at 180 °C. However, when *cis*-Ru(acac)$_2$(PPh$_2$py)(PhCN) was used under catalytic conditions to hydrate benzonitrile, the complex was catalytically active. From this study, the authors concluded that *cis*-Ru(acac)$_2$(PPh$_2$py)(PhCN) was not part of the catalytic cycle. They instead proposed that, because the conversion occurred only when excess nitrile ligand was added, one of the acac ligands partially dissociates during hydration. The dissociation enables the nitrile ligand to coordinate to the Ru, and hydration proceeds (Fig. 4).

Although the proposed mechanism is certainly viable, further experiments could help to confirm the proposed pathway. If dissociation of the ligand is necessary then changing the sterics or electronics of the ligand should influence the rate of hydration. Using an acac ligand containing bulky or electron-withdrawing groups should increase the rate of ligand dissociation, giving a faster catalyst. Utilizing NMR spectroscopy to investigate the position of the ligands during hydration would also provide more information about the active catalytic species. The use of ^{31}P NMR would help to confirm this mechanism. The ^{31}P{^{1}H} NMR signal of *cis*-Ru(acac)$_2$(PPh$_2$py)$_2$ is at 57.9 ppm in C_6D_6. If one of the phosphine ligands dissociates, a second signal should appear upfield for the free phosphine ligand. (The ^{31}P{^{1}H} NMR signal of free PPh$_2$py is at −3.9 ppm in $CDCl_3$ [102].) If one of the acac ligands partially dissociates then a second signal should appear close to 57 ppm to indicate that the two phosphine ligands are no longer equivalent but that both are still coordinated to the Ru.

Šmejkal and Breit followed up on the investigation of *cis*-Ru(acac)$_2$(PPh$_2$py)$_2$ by synthesizing the complexes *cis*-Ru(acac)$_2$(L)$_2$, where L = 6-diphenylphosphini-*N*-pivaloyl-2-aminopyridine (see complex **16**) or 3-diphenylphosphinoisoquinilone (see complex **17**) [53]. These complexes were designed as a part of an investigation into the formation of bidentate ligands via self-assembly, in this case through the formation of one or more hydrogen bonds between the ligands. The hydrogen-bonding ability of the ligands was also anticipated to be capable of increasing the rate of hydration by activating nearby water molecules toward nucleophilic attack of coordinated nitriles. The catalytic hydration of the model substrate 4-methylbenzonitrile was investigated using **16**, **17**, and the mixed-ligand complex **18** at 120 °C and 1% catalyst loading in 1,2-dimethoxyethane. The turnover frequencies of hydration decreased in the order **17** (20 h^{-1}) > **18** (5 h^{-1}) > **16** (not reported). Catalyst **16** promoted less than 5% conversion of the nitrile after 20 h. The lower catalytic activity of the aminopyridine-containing complex (**16**) was explained in three ways. First, the isoquinolone ligand is a weaker electron-donor than the aminopyridine ligand. The ruthenium center in the complexes containing the isoquinolone ligand (**17** and **18**) would therefore be better Lewis acids, and more capable of activating the nitrile carbon. Note, however, that the more Lewis acidic ruthenium of the isoquinolone complexes would also make the acac ligands more strongly coordinated. This result needs to be reconciled with Oshiki's proposal that partial dissociation of acac is necessary for nitrile hydration. The second explanation was that the isoquinolone ligands hydrogen bond to water better than the aminopyridine ligands, and, thus, **17** and **18** afford enhanced activation of the nucleophile relative to **16**. The last explanation is that the pyridine nitrogen in the aminopyridine complexes is capable of coordinating to the ruthenium. When the pyridine nitrogen is coordinated, the ruthenium does not have an open coordination site for the nitrile, so hydration ceases. Although the authors did not propose it, the hydrogen bonding between the amide nitrogen and the amide oxygen may also stabilize this structure, as in Fig. 5. This alternative bonding mode is not observed for the heteroligand complex, presumably because the hydrogen-bonding interaction between the ligands is more favorable than the formation of the pyridine–nitrogen–ruthenium bond.



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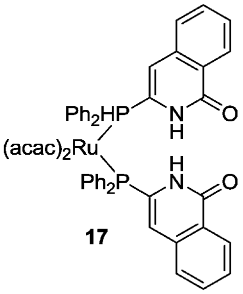

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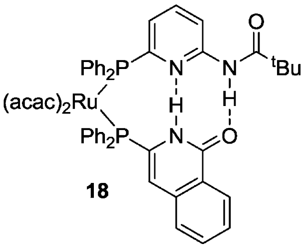

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Codierno et al. [56] investigated the complexes [$RuCl_2(\eta^6$-arene)(PR_3)] for nitrile hydration, where PR_3 is PTA (**19**), PTA-Bn (**20**), DAPTA (**21**), and TPPMS (**22**), and η^6-arene is benzene, *p*-cymene, 1,3,5-trimethylbenzene, and hexamethylbenzene (Fig. 6).

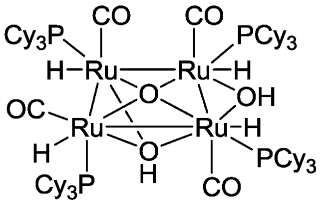
These complexes were all investigated for the ability to hydrate an aqueous solution of benzonitrile to benzamide at 100 °C and 5% catalyst loading. All were capable of hydrating benzonitrile, although the [$RuCl_2(\eta^6$-arene)(TPPMS)] (**22**) series displayed the lowest activity (TOF <1 h^{-1}). The authors hypothesized that the dramatic decrease in activity may be attributed to the fact that the phosphine ligand is unable to hydrogen bond to water to activate it, unlike the other catalysts investigated. The hydration activity of the other catalysts ranged from TOF = 1.0 h^{-1} to 9.9 h^{-1}, with [$RuCl_2(\eta^6$-C_6Me_6)(PTA-Bn)] (**20d**) displaying the highest activity. Additionally, as the arene ligand increased in steric bulk, the TOF within a series increased. For example, within the series [$RuCl_2(\eta^6$-arene)(PTA-Bn)] (**20**), the activity increased as follows: **20a** (2.0 h^{-1}) < **20b** (5.0 h^{-1}) < **20c** (5.0 h^{-1}) < **20d** (9.9 h^{-1}). Because increasing the steric bulk of the η^6-arene ligand will increase the rate of ligand dissociation, the rate-determining step in the hydration reaction may be amide dissociation. Additionally, having a more electron-donating η^6-arene ligand would make the metal center less Lewis acidic, which would make the Ru–amide bonds weaker.

Because **20d** displayed the highest activity of the Ru complexes investigated, it was used to hydrate a variety of other nitriles. These studies showed **20d** was tolerant of nitriles containing halide, nitro, ether, hydroxy, thioether, amino, ketone, aldehyde, ester, alkene, and alkyne substituents. The complex hydrated acrylonitrile with a high yield, and neither acrylonitrile nor acrylamide polymerized over the course of the reaction. Finally, **20d** was used in combination with microwaves because it was anticipated that microwaves would increase the rate of hydration. This was in fact the case. Thus, at 100 °C in an 80 W microwave at 5 mol% catalyst loading, benzonitrile was hydrated with a TOF of 15.7 h^{-1}, about 1.5 times faster than hydration in the absence of a microwave.

3.1.2.3. Nucleophilic attack by iminol. Unlike the [$RuH(\eta^5$-C_9H_7)dppm] catalyst (**11**) discussed in the previous section, the [$TpRuH(PPh_3)(CH_3CN)$] complex, **23**, reacted with water to form the aqua-acetamido complex [$TpRu(H_2O)(PPh_3)(NH(CO)CH_3)$], **24** (Fig. 7) [57]. It is believed that the reaction to form the acetamido complex is similar to the mechanism for the hydration with the [$RuH(\eta^5$-C_9H_7)dppm] complex, but after the acetamide ligand is formed, H_2 is evolved and is substituted with an aquo ligand. Both **23** and **24** were investigated for their ability to hydrate nitriles to amides at 120 °C with 0.1–0.2 mol% catalyst loading. The [$TpRu(H_2O)(PPh_3)(NH(CO)CH_3)$] complex converted to [$TpRu(CH_3CN)(PPh_3)(NH(CO)CH_3)$] (**25**) over time, which gradually converted to [$TpRu(PPh_3)(\kappa^2$-*N*,*O*-NH=CMeN=CMeO$^-$)], **26**.

Benzonitrile was also used to form phenyl analogues to the acetonitrile complexes **23**–**26**. The final *N*-imidoylimadato complexes (**26**) were the most stable species generated, and were the only catalytic species observed by ^{31}P and ^1H NMR spectroscopy at the end of the reaction. The *N*-imidoylimadato species are key intermediates in the proposed catalytic cycle (Scheme 13), which is supported by DFT calculations.

3.1.2.4. Cooperative multinuclear hydration. The tetranuclear ruthenium-μ-oxo-μ-hydroxo complex **27** was investigated for nitrile hydration based on the hypothesis that the close proximity of the ruthenium metal centers would lead to cooperative kinetics [62].



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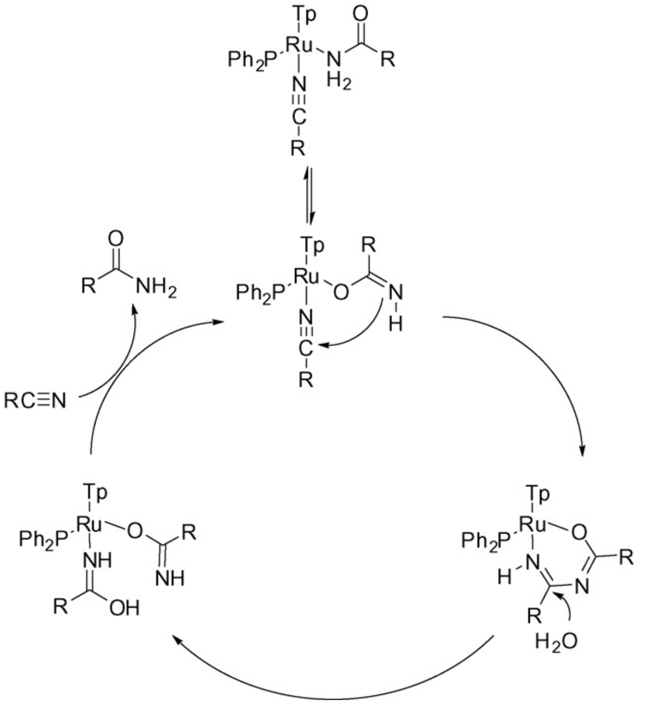
The complex was capable of hydrating nitriles at lower temperatures (80–90 °C) than the Ru(acac) complexes, with complete conversion of a variety of nitriles into the amide products with a 1–2% catalyst loading. Acrylic nitriles were also selectively hydrated under these conditions. Kinetic studies indicated at least three available and interacting substrate sites for nitrile coordination. Addition of excess tricyclohexylphosphine ligand resulted in a loss of the cooperative activity. Interestingly, the electronic nature



Scheme 13. Intramolecular attack of an O-bound imino ligand on a nitrile substrate.

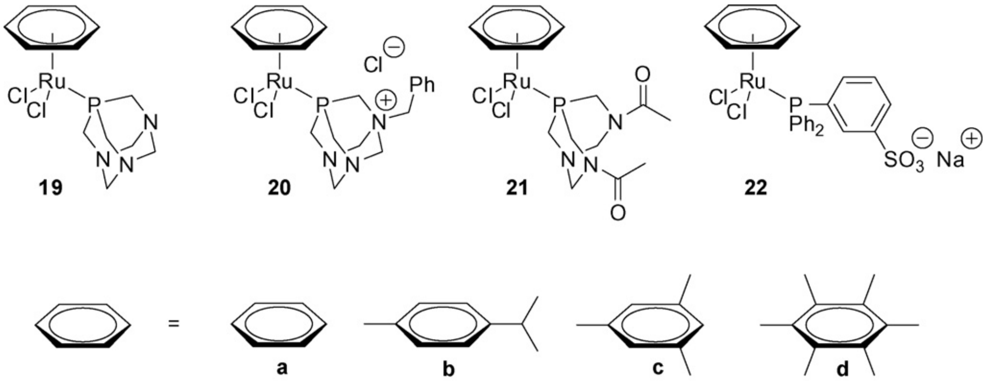


Fig. 6. Ru catalysts reported by Codierno et al.

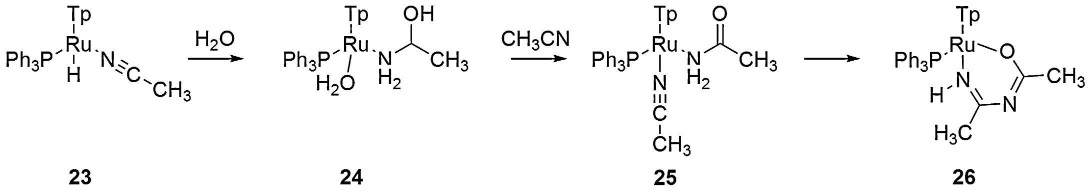


Fig. 7. Conversion of $[\mathrm{TpRuH(PPh_3)(CH_3CN)}]$ (Tp = trispyrazoleborate) to the Ru-*N*-imidoylimadato intermediate (**26**).

of the nitrile substituent played a role in whether the catalyst displayed cooperative or noncooperative activation. Nitriles that are electron-rich and nucleophillic were more likely to promote a noncooperative mechanism because they were capable of breaking up the cluster. The resulting monomeric ruthenium catalyst was proposed to be $(\mathrm{PCy_3})_2(\mathrm{CO})\mathrm{RuHCl}$ based upon several NMR studies, but the authors were unable to isolate the monomeric catalyst. There was no noticeable decrease in the rate of hydration when Hg^0 was added to the hydration mixture, which suggested to the authors that the catalyst is homogeneous.

3.1.3. Functional NHase mimics of Co^{3+}

As mentioned in the introduction to Section 3, acetonitrile hydration has been extensively investigated with tetra- and hexamine-cobalt complexes [40,41,43–45], in part because cobalt is contained within the active site of some nitrile hydratase enzymes. The NHase enzymes, employing either Fe^{3+} or Co^{3+} centers, contain two peptide amides and two cysteinate sulfurs in the equatorial plane, and an axially coordinated cysteinate sulfur (trans to the substrate binding site, Fig. 8). Both of the cyseinate sulfurs in the equatorial plane are oxidized, one to a sulfenate (SO) and the other to a sulfinate ($\mathrm{SO_2}$). (Several reviews have been published which focus on the study of both structural and functional NHase mimics, see [103–106].) While there are a large number of structural NHase mimics, only a few have been shown to be functional [65,66]. Mascharak and co-workers developed the NHase mimics $(\mathrm{Et_4N})_2[\mathrm{Co(PyPS)(CN)}]$ (**28**) and $(\mathrm{Et_4N})_2[\mathrm{Co(PyPS(SO_2))(CN)}]$ (**29**) [107], while Chottard and co-workers developed the octahedral complex $\mathrm{Na[Co(L\text{–}N_2SOSO)(tBuNC)_2]}$ (**30**) [108]. Both **28** and **29** rapidly lose CN^- in aqueous solution to form the complexes $(\mathrm{Et_4N})[\mathrm{Co(PyPS)(OH_2)}]$ and $(\mathrm{Et_4N})[\mathrm{Co(PyPS(SO_2))(OH_2)}]$, which are further deprotonated in basic conditions to form the active catalysts [65]. The TOFs for the hydration of acetonitrile at pH 8 using $(\mathrm{Et_4N})[\mathrm{Co(PyPS)(OH)}]^-$ and $(\mathrm{Et_4N})[\mathrm{Co(PyPS(SO_2))(OH)}]^-$ were $8\,\mathrm{h}^{-1}$ and $24\,\mathrm{h}^{-1}$, respectively. It was proposed that the increased rate of hydration for $(\mathrm{Et_4N})[\mathrm{Co(PyPS(SO_2))(OH)}]^-$ is due to the oxidation of the thiolate ligand, which decreases the $\mathrm{p}K_\mathrm{a}$ of the coordinated hydroxide ligand. The authors postulated that the hydration mechanism is similar to one of the mechanisms that was proposed for NHase (in which deprotonation of a metal-bound aqua ligand generates a metal-coordinated hydroxide ion that attacks a non-coordinated nitrile as in Scheme 14). Interestingly, the oxidation of the thiolate ligand also decreases the rate of cyanide dissociation.

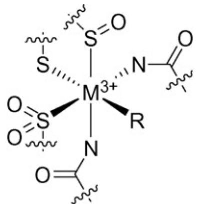
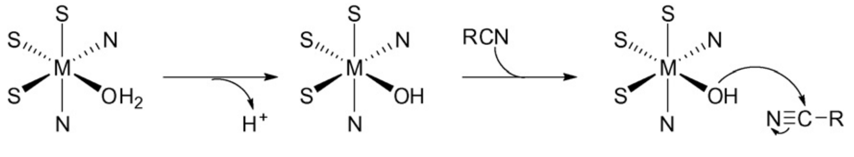
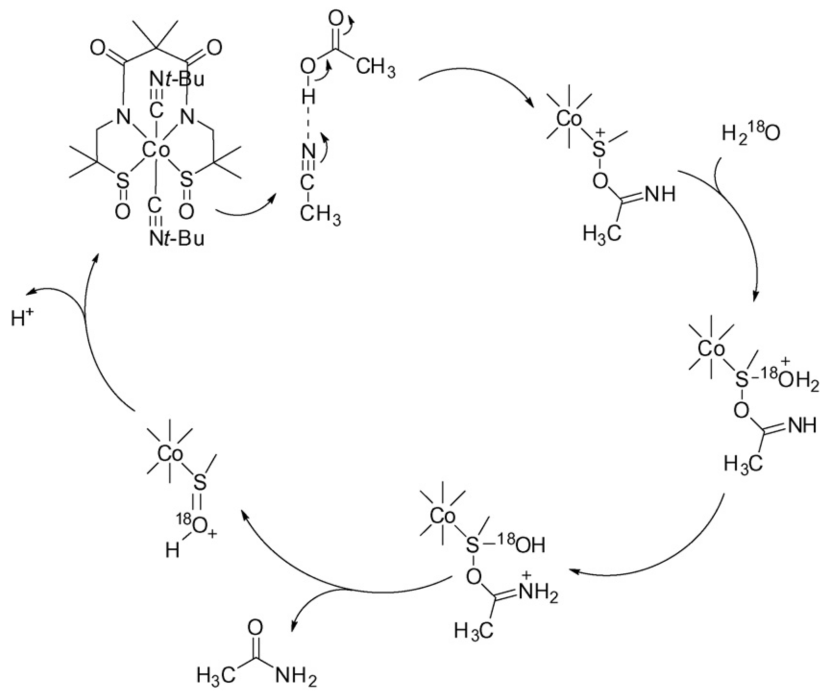


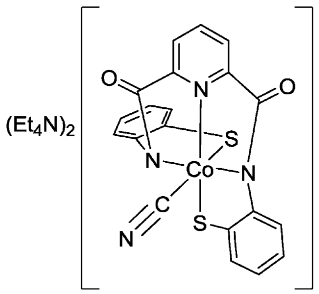
Fig. 8. Nitrile hydratase (NHase) active site M = Fe(III) or Co(III). R = NO ($\mathrm{Fe_{dark}}$) or $\mathrm{H_2O}$ ($\mathrm{Fe_{light}}$, Co).



Scheme 14. Nitrile hydration mechanism proposed by Mascharak and co-workers for **28** and **29**.



Scheme 15. Incorporation of ^{18}O into a sulfenato ligand via hydration of acetonitrile using **30**.



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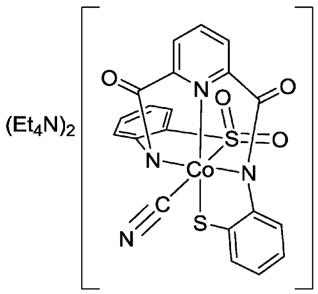

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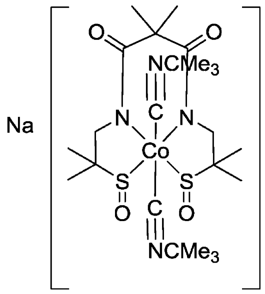

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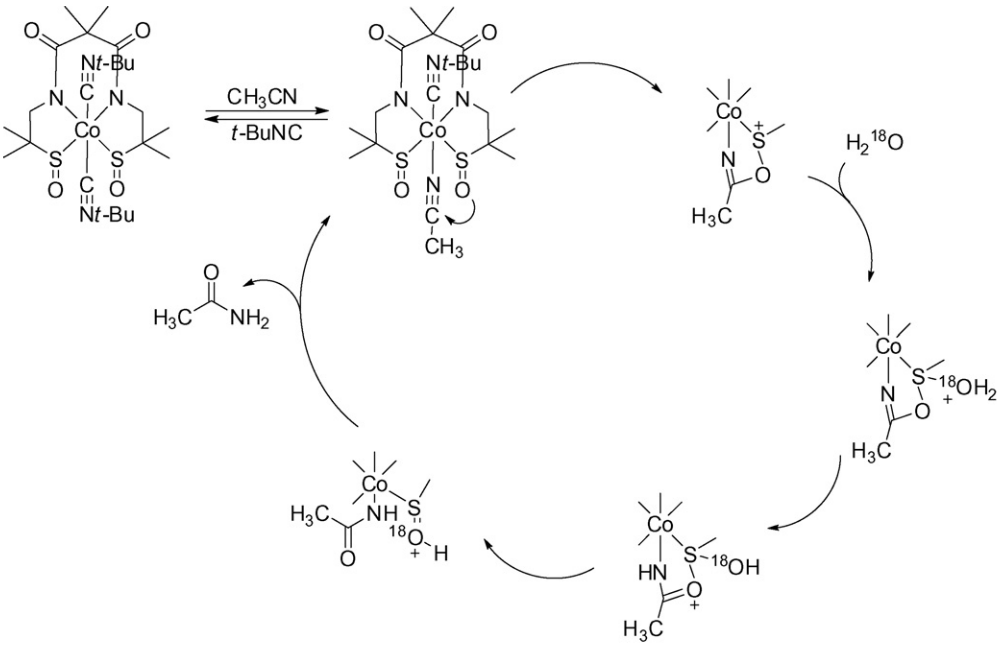
Na[Co(L–N_2SOSO)(tBuNC)$_2$], **30**, was also used in the hydration of acetonitrile. Unlike **28** and **29**, **30** hydrated acetonitrile under mildly acidic conditions at 4 °C [66]. The proposed mechanism does not involve coordination of the nitrile to the metal. Specifically, hydration was proposed to occur via nucleophillic attack of the sulfenato oxygen on the nitrile, followed by nucleophilic attack of water on the sulfenato-derived sulfur when acetic acid is used to buffer the solution (Scheme 15). This mechanism was supported by an ^{18}O isotope labeling study, which showed that when $H_2{}^{18}O$ was used to hydrate acetonitrile the ^{18}O was incorporated into the sulfenato ligand. When acetonitrile was not present, no ^{18}O was incorporated.

An alternative mechanism should also be considered. Previous work on the unoxidized complex showed that the isocyanide ligands are labile in dilute solution [109]. Additionally, oxidation of the thiols to sulfoxides weakens the Co–C bond of the isocyanide ligands, as indicated by an increase in the ν(CN) stretching frequency from 2140 cm^{-1} to 2375 and 2195 cm^{-1} [108]. If the isocyanide ligands are labile, it is possible that the nitrile can coordinate to the metal center (Scheme 16). The observation of **30** after hydration may imply that the catalyst is in the resting state when the isocyanide is coordinated. These observations could be examined by investigating similar complexes containing bulkier isocyanide ligands.

An additional point is that most nitrile hydration catalysts function by activating a coordinated nitrile to hydration. Although one could argue that the acidic conditions of the solution have the potential to activate the nitrile, a mechanism where the nitrile does not coordinate to, and is not activated by, the metal is nevertheless unusual. Note that, in both dilute acidic and dilute basic solutions, amide hydrolysis occurs faster than nitrile hydration. However, no carboxylic acid product was reported in Scheme 15, which strongly suggests that the nitrile is activated by coordination to the Co center.

3.1.4. *Rhodium and iridium acrylonitrile hydration*

Rauch and Nachtigall [70] reported that an acrylonitrile adduct of Rh, prepared by refluxing $RhCl_3$ in acrylonitrile, catalyzes the hydration of acrylonitrile to acrylamide in the presence of triphenylphosphine or a phosphite. In addition, small quantities of amide hydrolysis and C═C hydration products (acrylic acid and β-cyanoethanol, respectively, Eq. (1)) were formed. Interestingly, the addition of phosphine or phosphite to the reaction mixture increased the selectivity of the catalyst by halting the generation of both impurities (Eq. (2)). The cause of the improvement is unknown. Wilkinson's catalyst gave selective conversion of acrylonitrile without addition of the phosphite, but the Rh–acrylonitrile/phosphite mixture was far more reactive under



Scheme 16. Alternative mechanism for the hydration of acetonitrile using **30**.

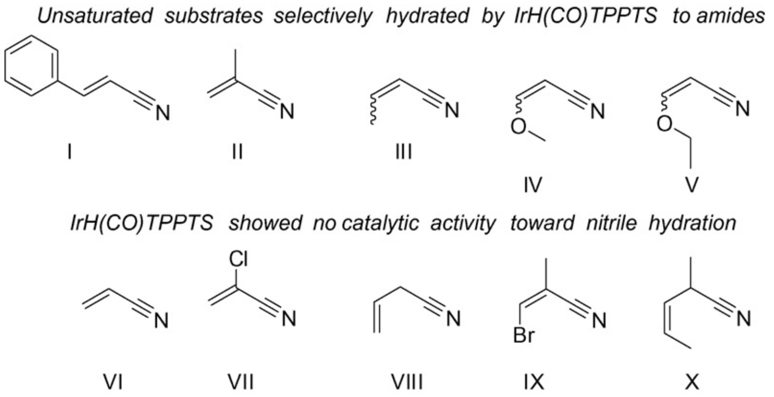
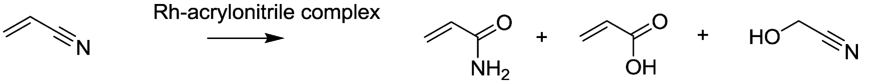
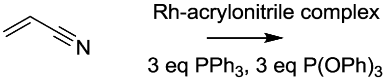


Fig. 9. Olefinic substrates reacted with IrH(CO)TPPS.

similar conditions (TOF = 0.50 h^{-1} versus 7.5 h^{-1}). The Ir analog, $IrCl(PPh_3)_3$, was even less active than the $RhCl(PPh_3)_3$ catalyst for the hydration of acrylonitrile (TOF = 0.50 h^{-1} and 0.23 h^{-1}, respectively), which is a general trend for all of the Rh and Ir catalysts noted in Table 1.

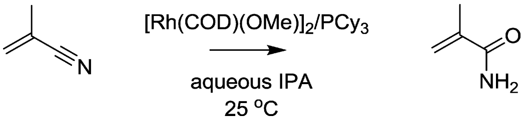


(1)



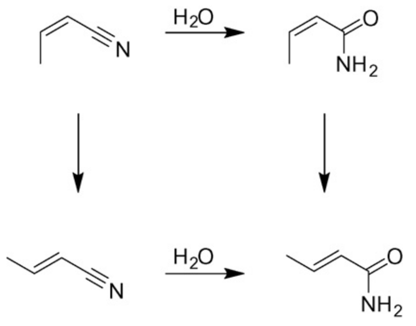
(2)

The recently reported methoxide ligated $[Rh(COD)(OMe)]_2/PCy_3$ complex showed remarkable activity at 25 °C and neutral pH [69]. Although the hydration mechanism was not probed, it is clear that the OR group plays a central role in promoting the acceleration. Thus replacement of the Rh catalyst with the $[Rh(COD)(OH)]_2$ analog gave a slightly lower yield in the hydration of benzonitrile (74% yield of benzamide in 17 h versus 90%). In addition, $[Rh(COD)(Cl)]_2$ and [Rh(COD)(acac)] displayed little activity. The mild reaction conditions were applicable to a range of nitrile substrates including aliphatic, aromatic, heteroaromatic, and olefinic substituents, and the hydration of methylacrylonitrile proceeded cleanly to 99% conversion in 24 h using 1 mol % Rh in aqueous isopropanol solvent (Eq. (3)). In a different report, TPPTS was used in combination with $[Rh(COD)Cl]_2$ to achieve impressive rates of acetonitrile hydration in water, also at ambient temperature (TOF = 31 h^{-1}). However, a large excess of base (10 equiv. with respect to Rh) and 80 psi N_2 were required. With $[Rh(COD)(OMe)]_2/PCy_3$, base was only employed to improve turnover in the hydration of very bulky nitriles such as trimethylacetonitrile and dinitrile substrates.



(3)

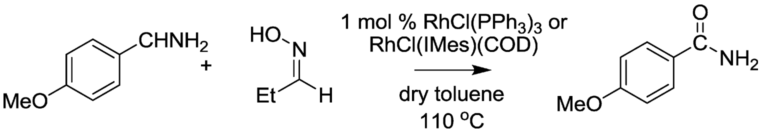
It is noteworthy that the water-soluble IrH(CO)TPPTS complex showed activity only with selected olefinic nitriles, including methylacrylonitrile [71]. (See Fig. 9 for a list of substrates that could be hydrated regioselectively and those that were unreac-



Scheme 17. Hydration of *cis*- and *trans*-$CH_3CH{=}CHCN$ catalyzed by IrH(CO)TPPTS.

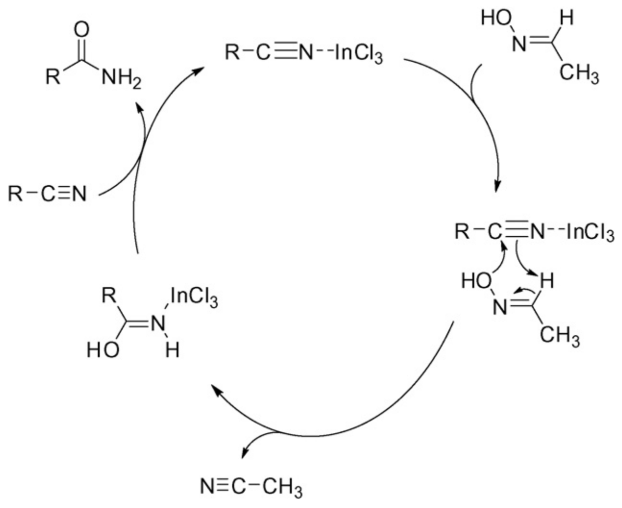
tive toward hydration.) The difference in reactivity between the substrates did not follow any clear trend, and the reason for the selectivity is not known. The IrH(CO)TPPTS complex can coordinate $C{=}C$ functional groups, which may impact hydration catalysis. For example, it was noted that substrates III and VIII were isomerized in the presence of the Ir catalyst. When a mixture of *cis*- and *trans*-III was reacted with the catalyst, the initial rate of hydration was faster for the *trans* isomer, and concomitant isomerization of the *cis*-olefin to *trans*-olefin was observed, leading to *trans*-amide as the final reaction product (Scheme 17). In addition, with substrate VIII, $CH_3CH{=}CHCONH_2$ was the only product detected after 24 h, indicating isomerization of $CH_2{=}CHCH_2CN$ to $CH_3CH{=}CHCN$ followed by rapid hydration of the nitrile. The Ir-catalyzed olefin isomerization, likely proceeding by reversible insertion of the olefin group into an Ir hydride, indicates extensive interaction between the Ir center and the olefin functionality. Furthermore, when $HC{\equiv}C(CH_2)_3CN$ was used, oligomeric products were recovered from the reaction mixture, and no hydration was observed. In the latter case, the alkyne functionality may have a greater affinity for the metal center than the nitrile, and preferential η^2-olefin coordination may prevent activation of the nitrile carbon. Competitive binding of the olefinic group in acrylonitrile also derailed selective conversion with several Pt bis(phosphine) and Pt^0 phosphine catalysts (vide infra). It should be noted that dissociation and oxidation of the TPPTS ligand from the IrH(CO)TPPTS complex was observed during catalysis, even though the reactions were carried out under an N_2 atmosphere.

3.1.4.1. Hydration of nitriles with oximes. Lee et al. [110] recently extended the utility of Wilkinson's catalyst to the anhydrous hydration of nitriles using aldoxime as the water source (Eq. (4)). In their report, $RhCl(PPh_3)_3$ and the Ru N-heterocyclic carbene complex RhCl(IMes)(COD) (where IMes = *N*,*N*-bis(2,4,6-trimethylphenyl)imidazole) promoted the hydration of *p*-methoxybenzonitrile to *p*-methoxybenzonitrile using 3 equiv. of propionaldoxime in good yield (87–89% yield, TOF = 14.5 h^{-1}, Eq. (3)). The activity of the two Rh catalysts was nearly identical. Unsaturated, aliphatic, and keto nitriles, as well as nitriles containing common alcohol protecting groups (such as TBS, THP, and MOM) were also hydrated in excellent yield (>75%) using 5 equiv. of commercially available acetaldoxime and $RhClPPh_3$.



(4)

The Lewis acid salts $InCl_3$, $FeCl_3$, BF_3, and $ZrCl_4$ also activated nitriles toward nucleophillic attack from the hydroxyl group of the aldoxime [111]. The best catalyst was $InCl_3$, which was used to hydrate benzonitrile to benzamide (3 h, refluxing toluene, 3 equiv. of acetaldoxime, 5 mol% catalyst loading, 98% yield). The hydration of acrylonitrile gave acrylamide in 78% yield at room temperature after 24 h. The proposed mechanism for hydration is a concerted heterocyclic rearrangement between the activated nitrile and the aldoxime, followed by loss of acetonitrile, then subsequent tautomerization of the imine to the amide (Scheme 18).



Scheme 18. Proposed mechanism for the anhydrous catalytic hydration of nitriles using aldoximes.

$Pd(OAc)_2/2PPh_3$ was used in combination with acetaldoxime in dry toluene to hydrate a variety of nitriles, including acrylonitrile, with moderate to excellent yield. Acrylonitrile was hydrated in 91% yield in 3 h using 2 equiv. of acetaloxime and 10 mol% catalyst loading in a refluxing water/ethanol solution. Toluene and dry ethanol were also viable reaction solutions. A wide variety of Baylis–Hillman adducts of acrylamide were also synthesized using the $Pd(OAc)_2/2PPh_3$ system [111,112].

One significant drawback of this system is that excess alkoxime is required for catalytic efficiency. The reaction became less efficient using lower ratios of acetaldoxime due to competitive hydration of the acetonitrile product. However, the optimized reaction conditions gave impressive results, and the acetonitrile product was easily removed upon addition of water for most of the nitrile substrates investigated. Finally, it is noted that the use of aldoximes as an anhydrous nitrile hydration reagent is promising for hydration of nitriles containing water-sensitive substituents or those that easily degrade in water.

Pombeiro and co-workers also investigated the use of oximes for the hydration of nitriles [119]. Their study showed that Zn(II) salts, when used in combination with ketoximes in aqueous solutions, were capable of hydrating a variety of alkyl, benzyl, and aliphatic nitriles. $Zn(NO_3)_2{\cdot}6H_2O$ was identified as the best Zn(II) salt when used in combination with 2-propanone oxime. TOFs between 4.5 h^{-1} and 45.0 h^{-1} were observed (using 0.66 mol% catalyst loading and 2.64 mol% ketoxime under reflux), with *p*-methoxybenzylnitrile giving the best rate. However, the increase in the rate was expected due to the fact that the amide product precipitates out of solution. This may indicate that the amide product coordinates to the Zn(II) salt, giving product inhibition. In all cases, 5–9% carboxylic acid byproduct was formed, despite the beutral conditions used. The more homogenous acetonitrile mixture had the greatest amount of carboxylic acid impurity, at 20%.

It is of interest to note that the ketoxime acts catalytically in this system. The best hydration results were obtained when 4 equiv. of ketoxime:Zn were used. The proposed mechanism involves the coordination of the nitrile to the Zn, followed by nucleophillic attack of the oxime on the nitrile carbon. The resulting [Zn]–NH═C(R′)–O–N═CR$_2$ imino intermediate is then hydrolyzed to produce the amide and regenerate the Zn-oxime catalyst. An advantage of using the ketoxime is that, unlike the aldoxime reagents, no nitrile byproduct is produced and only catalytic amounts of ketoxime are required.

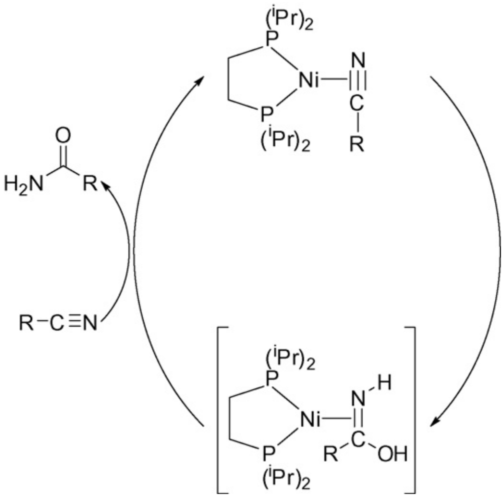
3.1.5. η^2-Activation at Ni^0

The Ni^0 complex [(dippe)Ni(η^2-NCR)] was investigated as a catalyst for the hydration of acetonitrile and benzonitrile [60]. The complex is unusual in that it coordinates to nitriles in an η^2-fashion, unlike most nitrile hydration catalysts, which activate nitriles in an η^1-fashion. Hydration is believed to occur via an intermolecular nucleophillic attack of water on the η^2-nitrile, followed by a ligand substitution of the resulting amide for another nitrile (Scheme 19).

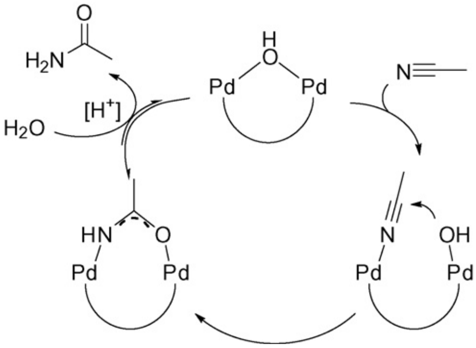
The η^2-coordination of the nitrile was confirmed by ^{31}P NMR studies, which showed two different signals, indicating the phosphines were in different coordination environments. A potassium iodide poisoning study was carried out in order to examine whether it would effect the hydration of the nitrile. (A change in the oxidation state of the nickel would result in the formation of a Ni^{2+}-iodide complex.) However, there was no change in the rate of hydration in the presence of potassium iodide, which was taken to indicate that the oxidation state of the nickel does not change from Ni^0 to Ni^{2+}. Because the oxidation state of the Ni does not change, it was hypothesized that the coordination mode of the nitrile (i.e., η^2 versus η^1) does not change over the course of the reaction.

The hydration of benzonitrile was conducted under both basic and neutral conditions, and hydration was faster under neutral conditions (pH 7, 180 °C, 0.04 mol% [(dippe)Ni(η^2-NCPh)]) with a TOF of 14 h^{-1} and a TON of 984. In contrast, under basic conditions (pH 10, 180 °C, 0.04 mol% [(dippe)Ni(η^2-NCPh)]) the TOF was 5 h^{-1} and the TON was 354. As a result, the rate-limiting step was proposed to be a concerted *N*,*N*-dihydro-*C*-oxi-biaddition, where the proton-transfer and nucleophillic attack of water on the nitrile occur simultaneously.

The hydration of benzonitrile was also investigated with [(dtbpe)Ni(η^2-NCPh)] and [(dcype)Ni(η^2-NCPh)] at pH 7, 180 °C, and 0.04 mol% catalyst loading, with [(dtbpe)Ni(η^2-NCPh)] giving a TOF of 6 h^{-1} and TON of 467; [(dcype)Ni(η^2-NCPh)] had a TOF of 9 h^{-1} and a TON of 651. The rate of hydration was influenced by the size of the phosphine ligands (the TOF decreased as the phosphine bulk increased), as expected for side-on coordination of the nitrile. Ligand electronic effects on the rate of hydration were not investigated.



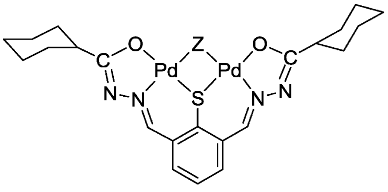
Scheme 19. η^2-Activation of a nitrile ligand.



Scheme 20. Intramolecular hydration of acetonitrile to acetamide using bimetallic catalysts **31** and **32** and acid co-catalyst.

3.1.6. Bimetallic palladium catalysis

The thiolate-bridged, bimetallic Pd catalysts **31** and **32** (where Z = MeCONH), investigated by McKenzie and Robson in 1988 [73], are still the most effective palladium hydration catalysts reported to date. Using acetonitrile as the substrate and Z = MeCONH, over 4000 turnovers at rates greater than 80 h^{-1} and 30 h^{-1} were achieved with **31** and **32**, respectively, in acidic, aqueous solution.



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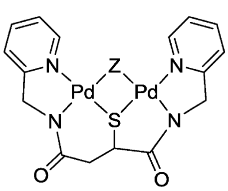

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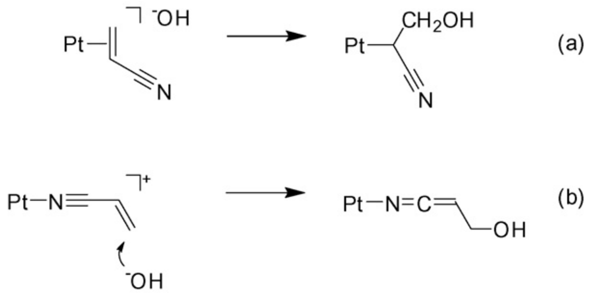
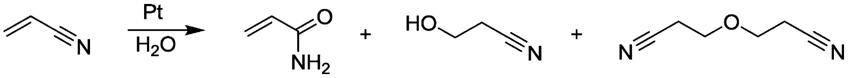
A binuclear mechanism involving attack of a hydroxo ligand on the nitrile ligand bonded to the second Pd center was proposed (Scheme 20). The equilibrium between the imino- and hydroxo-bridged Pd dimers lies in favor of imino complexation, and acid was required to catalyze the release of the amide product. However, high acid concentrations led to protonation of the hydroxo nucleophile and a reduction in the rate of hydration, consistent with the intramolecular mechanism. Selective conversion of acrylonitrile to acrylamide using catalyst **32** and HBF$_4$ as the co-catalyst was attributed to the preorganization of the nitrile and hydroxo reactants in the bimetallic intermediate. Unfortunately, even at optimal acid:catalyst ratios, product inhibition was observed.

3.1.7. Reactivity of Pt with acrylonitriles and cyanohydrins

Out of all of the catalysts that have been examined with unsaturated nitrile substrates, the Pt-bis(phosphine) complexes (i.e. *trans*-[PtH(H$_2$O)(PMe$_3$)$_2$][OH], Pt^0(P)$_2$, and [Pt(OH)R(P$_2$)]) are the least selective for hydration of the C≡N bond [68,79–81]. In all of these cases, Pt-catalyzed addition of water to acrylonitrile results in hydration of the C═C bond and conjugate addition of the alcohol product to the olefin starting material to give β-cyanoethanol and β-dicyanoethyl ether byproducts, in addition to the desired acrylamide product (Eq. (5)). The dicyano product CH$_2$C(CN)CH$_2$CH$_2$CN formed by dimerization of acrylonitrile was also observed in reaction mixtures of the Pt^0 phosphine catalysts.



Scheme 21. Key steps in the proposed olefin hydration pathways involving intermolecular attack (a) on an η^2-bound olefin and (b) on an N-bound substrate.



(5)

Two pathways were proposed for olefin hydration, as shown in Scheme 21. The first route (Scheme 21a) involves hydroxide attack on an η^2-bound olefin, and, in the second pathway, hydroxide is added to the β-carbon of the N-bound substrate (Scheme 21b).

Olefin coordination is thought to be operative in *trans*-$[PtH(H_2O)(PMe_3)_2][OH]$ and Pt^0R_2 catalysis [80,81]. In the Pt(II)-bis(phosphine) systems, η^2-olefin binding is indicated by deuterium incorporation into the α-position of the β-cyanoethanol and β-dicyanoethyl ether products when using labeled *trans*-$[PtD(Cl)(PMe_3)_2]$ pre-catalyst. Note that no deuterium incorporation would be expected in the conjugate Michael addition of OH^- to the N-bound substrate. In the case of $Pt^0(R)_x$ catalysts, the impeding effect of steric bulk implicates η^2-olefin coordination. Thus, the bulkier $Pt[PPh(t\text{-}Bu)_2]_2$ and $Pt[P(i\text{-}Pr)_3]_3$ catalysts exhibit much greater selectivity for the CN bond in crotonitrile ($CH_3CH{=}CHCN$, olefin/CN = 0.13 and 0.21, respectively) than in acrylonitrile (olefin/CN = 33 and 13, respectively). In contrast, when using the less sterically hindered $Pt(PEt_3)_3$ catalyst, comparable selectively was observed for the bulkier crotonitrile substrate (olefin/CN = 12.6) and acrylonitrile (olefin/CN = 8.0). The opposite trend was reported, however, for the Pt alkyl bis(phosphines), $[Pt(OH)R(L)_2]$ (where R = Ph or Me and L = PMe_2Ph, PPh_3, PEt_3, P^tBu_2Me, PCy_3, or DPPE). The bulkier phosphine ligands (P^tBu_2Me, PCy_3) favored olefin hydration, consistent with addition to the remote olefin group of the N-bonded structure (Scheme 21b).

The Pt-phosphine catalysts are all proposed to hydrate via a similar pathway that relies on formation of a very basic $[L_nPt\text{–}NCR]^+[OH]^-$ ion pair. Under the reaction conditions, Pt tris(phosphine) complexes are in equilibrium with Pt bis(phosphine) catalysts. Water oxidatively adds to the Pt^0 bis(phosphine) catalysts (Scheme 22 pathway a) to give *trans*-$[Pt(OH)(H)P_2)]$. Substitution of the hydroxo ligand for the nitrile, followed by intermolecular attack by the OH^- counterion leads to rapid hydration. The resulting amide products are reductively eliminated from the Pt center or hydrolyzed to afford labile Pt-amide linkages. The most active of these catalysts employ sterically unhindered phosphines and strong electron donors *trans* to the substrate binding site (compare Table 1 entries 61 and 62 or 63 and 71). Bulky ligands may slow the reaction rate by hindering nitrile association and/or approach of the nucleophile. The strong *trans* influence ligand likely facilitates OH^- and/or amide substitution, leading to very high turnover numbers in the range 1000–6000.

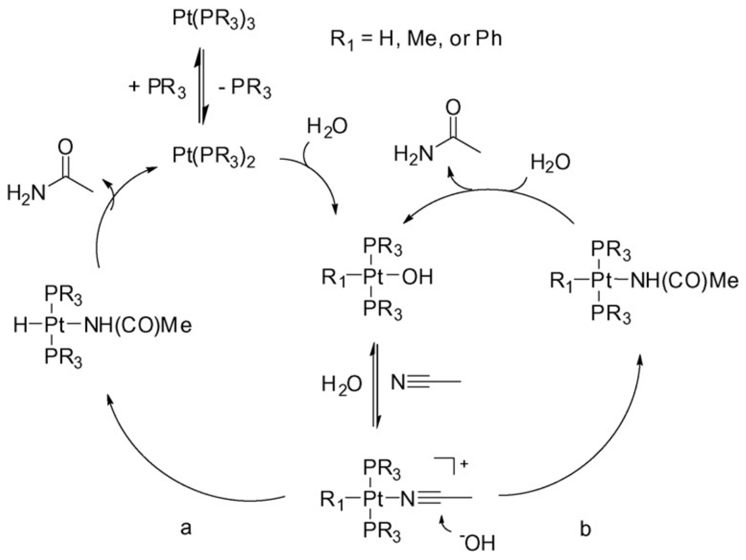
The Pt phosphinito catalyst reported by Parkins and co-workers, $[Pt(X)(PMe_2OH)\{(PMe_2O)_2H\}]$ (where X = H, Cl), incorporates a tethered hydroxo nucleophile, thereby eliminating the need for base [78,113]. The proposed mechanism for these complexes is shown in Scheme 23. In this scheme, the hydrido ligand is protonated in water to give a vacant coordination site for an incoming substrate. If the chloride complex is used, the chloride is substituted by water or nitrile upon addition of a chloride abstraction agent. Substrate coordination is followed by intramolecular nucleophilic attack of the phosphinito hydroxyl on the nitrile. Subsequent hydrolysis of the resulting five-membered iminol species affords the amide product and regenerates the catalyst. However, the phosphinito hydroxyl groups may simply be activating water toward nucleophilic attack of the nitrile, much like the Ruthenium complexes that contain ligands capable of hydrogen bonding to water. This conjecture is supported by the fact that increasing the steric bulk of the phosphinito ligands decreased the rate of nitrile hydration. Additionally, substitution of one of the PMe_2OH ligands for PMe_2Ph resulted in a drastic decrease in the rate of hydration, consistent with attack of the phosphinito hydroxyl group and ligand-assisted water activation.

The Pt phosphinito system catalyzes the selective hydration of a wide range of other nitriles including very bulky nitriles, unsaturated nitriles (such as acrylonitrile), and nitriles containing acid- and base-sensitive functional groups, such as those commonly used as protecting groups [114]. The Pt phosphinito catalyst also shows some activity toward lactonitrile and 2-hydroxybutryonitrile cyanohydrin substrates. The rates of cyanohydrin hydration are slow in comparison to those of all other nitriles, and fewer turnovers are achieved with relatively high catalyst loadings [96]. It should be noted that $[PtCl(PMe_2OH)\{(PMe_2O)_2H\}]$ was used as the pre-catalyst in cyanohydrin hydration investigations because it was the fastest reported hydration catalyst. Comparison of the hydration reactivity of cyanohydrins to that of other nitriles demonstrated that the low reactivity of the α-hydroxynitrile substrates is not due to the steric or electronic consequences of the hydroxy group on the α carbon. In fact, the cyanohydrin lactonitrile exhibited initial rates that were comparable to those of other nitriles containing electron-withdrawing substituents, such as β-hydroxypropionitrile. This result demonstrates that the electronic character of the nitrile carbon in cyanohydrins is not unusual in comparison with other nitriles. DFT calculations corroborated this empirical finding, and, in fact, indicated that the intermolecular nucleophilic attack on lactonitrile was more favorable than on the β-hydroxypropionitrile isomer.

The reduced reactivity of cyanohydrins is instead due to liberation of HCN from the cyanohydrin substrate, the coordination of which leads to deactivation of the catalyst. No evidence of metal-mediated dehydrocyanation was observed; however, coordination of the free cyanide to the transition metal encourages greater dehydrocyanation by removing HCN from the equilibrium. Irreversible binding of cyanide, as evidenced by a linear decrease in the rate of acetonitrile hydration upon addition of cyanide [96], ensured complete catalyst poisoning. Because the dissociation of cyanohydrins in aqueous solution is inevitable, cyanide coordination may explain the poor catalytic efficiency noted for cyanohydrin hydration using other transition metal nitrile hydration catalysts, including heterogeneous catalysts and enzymes. Note that if cyanide binding were reversible, catalytic turnover could be improved by regulating the concentration of free cyanide ions and cyanohydrin substrate in solution, as was done in the biocatalytic cyanodryin hydration process developed by Tamura and previously discussed in Section 2.1.2.

3.2. Cyanohydrin dissociation in aqueous solution

The rate of cyanohydrin formation and degradation was investigated for selected cyanohydrins in aqueous solution, and the



Scheme 22. General base catalysis of a Pt-activated nitrile hydration reaction.

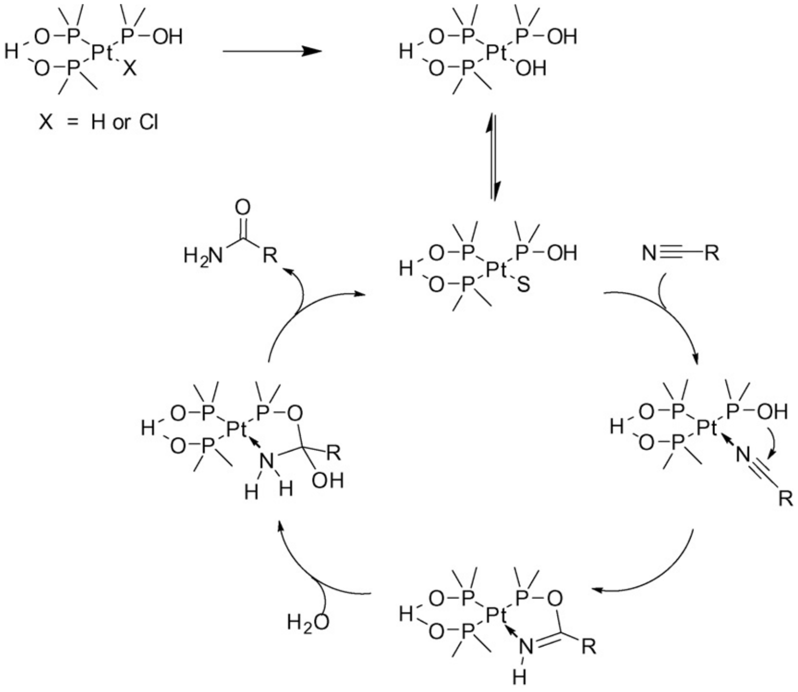
equilibrium constants and rate constants are summarized in Table 3. In Table 3, K_1 represents the equilibrium established between the cyanohydrin, aldehyde or ketone, and hydrocyanic acid in aqueous solution at pH <7.5 (Eq. (6)); K_2 is used to denoted the equilibrium dissociation of the alkoxide conjugate base, the aldehyde or ketone, and cyanide ions in basic solution of pH >8 (Eq. (7)).

$$K_1 = \frac{[\mathrm{RR'CO}][\mathrm{HCN}]}{[\mathrm{RR'C(OH)CN}]} \tag{6}$$

$$K_2 = \frac{[\mathrm{RR'CO}][\mathrm{CN^-}]}{[\mathrm{RR'C(O^-)CN}]} \tag{7}$$

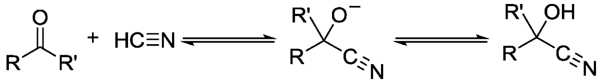
As a general trend, cyanohydrins containing bulkier substituents degrade more quickly [115]. This result is especially apparent when comparing the cyanohydrins derived from acetaldehyde, benzaldehyde, and acetone. Also note that electron-withdrawing groups stabilize the cyanohydrin. Additionally, the rate of cyanohydrin degradation is much faster under basic conditions. For a more detailed analysis of the various cyanohydrin equilibria, see Refs. [115,116].

The effect of base on the position of the equilibrium and the rate of cyanohydrin dissociation in water can be understood by considering the mechanism of cyanohydrin formation. Cyanohydrins are synthesized by nucleophilic addition of cyanide to an aldehyde or ketone carbonyl group followed by protonation of the resulting alkoxide (Eq. (8)). Therefore, base catalyzes the forma-



Scheme 23. Hydration of nitriles via transfer of a hydroxo substituent from a phosphinito ligand.

tion and degradation of cyanohydrins. In water, the dissociation of hydrocyanic


(8)

acid to free cyanide ions is encouraged by base and shifts the position of the equilibrium toward the dissociation products [117]. However, in various non-aqueous solvents, such as acetone and butanol, the presence of triethylamine did not alter the dissociation equilibrium of acetone cyanohydrin as it does in water [117]. Triethylamine even decreased dissociation of acetone cyanohydrin in non-polar solvents such as benzene, carbon tetrachloride, and dioxane. The equilibrium effects observed in non-aqueous solvents were attributed to the complex interplay of solvent pK_a, hydrogen-bonding ability, and influence on cyanohydrin-amine and/or HCN-amine complexation.

Cyanohydrin can be protected to circumvent the problem of cyanide poisoning. Shariff et al. showed that a bimetallic titanium catalyst **33** can convert aldehydes into non-racemic cyanohydrin acetates using potassium cyanide and acetic anhydride. The resulting nitriles were then hydrated to the corresponding amides using $[PtH(PMe_2OH)((PMe_2O)_2H)]$ as a catalyst (Fig. 10) [118].

The (R)- or (S)-cyanohydrin acetates were produced using **33**, or the enantiomers of **33**, with 64–89% e.e. The acetate is stable under the hydration conditions, and the resulting α-acetoxy amides were also non-racemic. Note, however, that no attempt was made in this study to hydrate cyanohydrin acetates derived from ketones. This would be an important study because, as established earlier, several desired acrylic products can be obtained from ketone-derived cyanohydrins.

4. Application of key insights to the rational design of the next generation of nitrile hydration catalysts and future outlook

Based upon the work summarized in Section 3, the best nitrile hydration catalysts are those designed to activate a nitrile and a nucleophile simultaneously, thereby arranging them for facile addition. In early studies, this design feature was achieved by the catalytic activation of water to give a metal-bound hydroxo nucleophile and by coordination of the nitrile substrate to the same metal center (or a second metal center in a multinuclear system). Such an arrangement facilitates an *intramolecular* attack. In the case of the Pt(II) catalyst **34**, nitrile substrates were organized *cis* to a hydroxy-containing phosphinito ligand, also leading to intramolecular nucleophilic attack with unprecedented rates. In the last decade, a new mechanism has emerged from explorations of Ru^{2+}-catalyzed hydration wherein water is activated by hydrogen bonding to an inner-sphere ligand, instead of by direct coordination to the metal center. This activation strategy has also led to impressive rate accelerations, and it will be interesting to see how it is employed in future advancements.

Rate accelerations that rely on organization of the nitrile functionality in close proximity to a hydroxide nucleophile also lead to better functional group tolerance and better regioselectivity, especially when neutral conditions are employed. This is best demonstrated by examples with Pt catalysts. Thus, hydration of acrylonitrile using the Pt phosphinito catalyst **34** proceeds rapidly and with high selectivity (>99.7%) to acrylamide. However, when general base catalysis occurs, as with the Pt bis(phosphine) complexes (Scheme 22), the olefin group is hydrated either by hydroxide attack of the η^2-coordinated olefin or by conjugate addition to the N-bound substrate. In some cases, competitive olefin coordination may also prevent or inhibit activation of the nitrile functionality, and, as a result, careful consideration should be given in the selection of the ligand employed *trans* to the nitrile coordination site. Studies of the Pt catalysts demonstrated the importance of having a strong *trans* influence ligand in order to facilitate dissociation of the amide product and to attain high catalytic turnover. However, strong σ donors such as H^- or R^- may also favor coordination of a weak σ-donating olefin functionality over the nitrile group. In this regard, phosphines, which are also good π-acceptor ligands, are superior *trans* effect ligands because they favor coordination of the nitrile group.

The hydration of cyanohydrins, on the other hand, appears to be inhibited by dissociation of the cyanohydrin to HCN, with subsequent catalyst poisoning. As a result, a nitrile hydration catalyst resistant to cyanide poisoning must be identified. The lack of sensitivity of the NHase mimics **28** and **29** to cyanide, as suggested by the hydration of acetonitrile in the presence of CN^-, makes these two complexes potential candidates for hydration of cyanohydrins. However, while these two complexes have the potential to hydrate cyanohydrins, they are not without inherent problems. First, synthesis of the active catalyst requires splitting the $(Et_4N)_2[Co_2(PyPS)_2]$ dimer or the $(Et_4N)_2[Co_2(PyPS(SO_2))_2]$ dimer to the monomeric cyano complex using $(Et_4N)CN$. When the cyanide ligand dissociates from the monomer in aqueous solution, the dimer is slowly regenerated (Scheme 24) [65]. The dimer is not active for hydration.

Second, the catalyst is only active when the pH is greater than the pK_as of the complexes, which are 8.3 ± 0.03 for

Table 3
Thermodynamic and kinetic data for selected cyanohydrins.

Aldehyde/ketone	K_1	K_2	k_2 (s^{-1})	k_{-2} ($M^{-1}\,s^{-1}$)
Formaldehyde[a,b]	1.09×10^{-9}	3.29×10^{-8}	1.15×10^{-2}	3.50×10^{5}
Acetaldehyde[a,c]	2.74×10^{-5}	5.16×10^{-3}	3.54	687
Acetone[a]	7.16×10^{-2}	68.5	272	3.97
Benzaldehyde[a,d]	5.14×10^{-3}	0.705	82.4	114
Benzaldehyde[d,e]	4.24×10^{-3}	0.183	13.2	68.4
4-Dimethylaminobenzaldehyde[e]	0.206	5.00	59.2	0.962
4-Methoxybenzaldehyde[e]	3.06×10^{-2}	2.12	22.5	11.6
4-Methylbenzaldehyde[e]	8.77×10^{-3}	0.595	16.0	27.2
4-Chlorobenzaldehyde[e]	3.25×10^{-3}	0.139	26.4	130
3,4-Dichlorobenzaldehyde[e]	2.00×10^{-3}	5.78×10^{-2}	16.0	252
4-Nitrobenzaldehyde[e]	5.49×10^{-4}	7.09×10^{-3}	17.5	916

Equilibrium and rate constants for the reaction of aldehydes and acetone with cyanide in aqueous solution at 25 °C.

[a] Ref. [116]. Ionic strength: 0.05 M K_1 measured at pH 3.78–4.68. K_2 measured at pH >8.92.

[b] Initial concentrations: formaldehyde, 2×10^{-3} M; HCN, 2×10^{-3} M.

[c] Initial concentrations: acetaldehyde, 2×10^{-3} M; HCN, 2×10^{-3} M.

[d] The difference in K and k may be attributed to a difference in pK_a^{HCN} values used.

[e] Ref. [115]. Ionic strength: 1.0 M. K_1 measured at pH 2.55–7.50. K_2 measured at pH >11.8–13.0. Substrate concentrations: 4-H, 5×10^{-4} M; 4-Me_2N, 6×10^{-5} M; 4-MeO, 8×10^{-5} M; 4-Me, $(8–10) \times 10^{-5}$ M; 4-Cl, $(1–5) \times 10^{-4}$ M; 3,4-Cl, $(0.8–1) \times 10^{-4}$ M; 4-NO_2, $(1–2) \times 10^{-4}$ M.

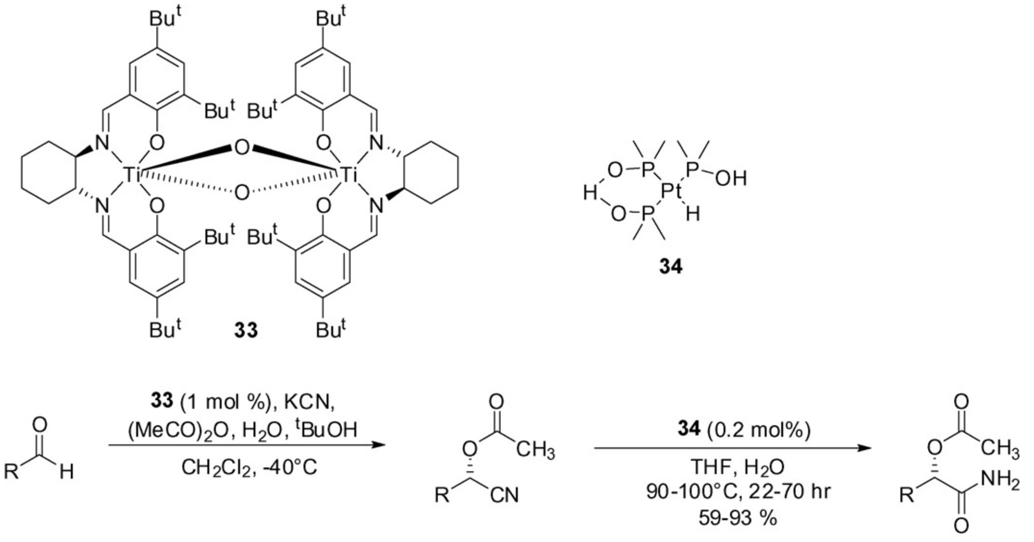


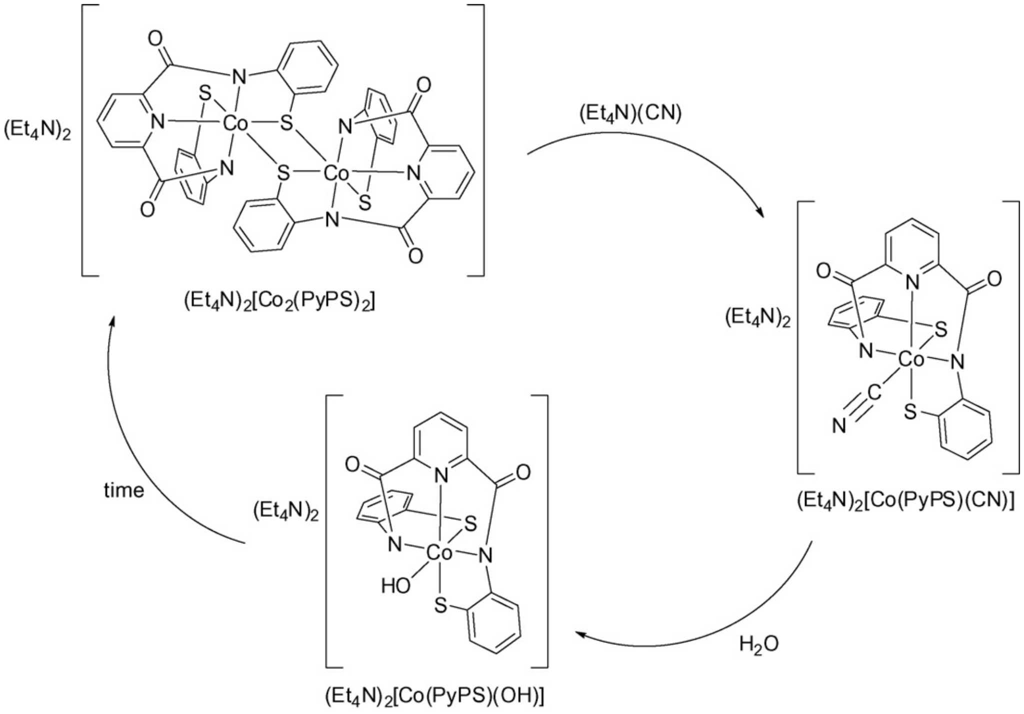
Fig. 10. Hydration of protected cyanohydrins.

$[Co(PyPS)(H_2O)]^-$ and 7.2 ± 0.06 for $[Co(PyPS(SO_2))(H_2O)]^-$. These basic conditions destabilize cyanohydrins [117], which makes these catalysts less promising for cyanohydrin hydration. If these catalysts are to be used for cyanohydrin hydration, future work should focus on making them active at lower pH, increasing the rate of hydration, and decreasing the rate at which the dimer forms to prevent the catalyst from self-quenching.

While questions about the mechanism of hydration by complex **30** have been raised, this catalyst was shown to hydrate acetonitrile under acidic conditions and at low temperatures. These are the very conditions that stabilize cyanohydrins, which makes complex **30** promising as a cyanohydrin hydration catalyst. However, more work needs to be done to determine the substrate scope of the complex because its hydration ability has only been investigated with acetonitrile.

Co(III) NHase mimics are also limited by their very low catalytic activity and high propensity toward product inhibition. However, the electronic environment provided by the ligand scaffold used in these systems appears to be key to the observed reaction mechanisms. This dominant effect of the ligand environment has also been shown in NHase enzymes. In such case, the reactivity of the enzymes is controlled by the ligand scaffold. An interesting observation is that the hydration activity of Fe(III) NHase is unaffected by the substitution of Fe(III) by Co(III) [120]. Substitutions using other metal ions have not been explored, but this effect might be more broadly applied to other ligand scaffolds as well. It would be interesting to explore the reactivity of the ligands used for the NHase mimics with more reactive metal centers such as Ru(II).

As discussed in Section 3.2, the cyanohydrin dissociation equilibrium is highly solvent dependent, and water encourages the



Scheme 24. Dimerization of **28**.

dissociation. In fact, pure solutions of cyanohydrin substrates can be stored for months with the addition of <1% acid. Based on the negative impact of water, it is proposed that cyanohydrin dissociation and subsequent catalyst poisoning may be circumvented by the anhydrous hydration of cyanohydrins using alkoximes. Of course, the current alkoxime hydration route is not industrially viable due to the use of excess alkoxime and the stoichiometric generation of nitrile substrate. However, the demonstration of successful, efficient cyanohydrin hydration via anhydrous conditions would be very high impact, as it may serve as a platform for the development other more feasible anhydrous pathways.

In conclusion, the development of new catalysts for the hydration of nitriles is a field that has received considerable attention in the past several years. Of specific interest to industry is the environmentally friendly production of acrylic amides, which can be achieved by hydration of acrylic nitriles, or by hydration of cyanohydrins followed by dehydration of the resulting amide product. Although several homogeneous catalytic systems have been developed that are capable of selective hydration of nitriles in the presence of olefins, there is still a strong need for catalysts that are capable of hydrating cyanohydrins.

Acknowledgment

Acknowledgment is made to the NSF (CHE-0719171) for the support of research carried out in the authors' laboratory.

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Further reading

After the submission of this manuscript, two papers of particular relevance to the topic of nitrile hydration were published. See:

(a) R. García-Álvarez, J. Díez, P. Crochet, V. Cadierno, Organometallics 29 (2010) 3955.
(b) H.B. Ammar, X. Miao, C. Fischmeister, L. Toupet, P.H. Dixneuf, Organometallics (2010), doi:10.1021/om100674x.