ORGANOMETALLICS

Article

pubs.acs.org/Organometallics

Ruthenium-Catalyzed Rearrangement of Aldoximes to Primary Amides in Water

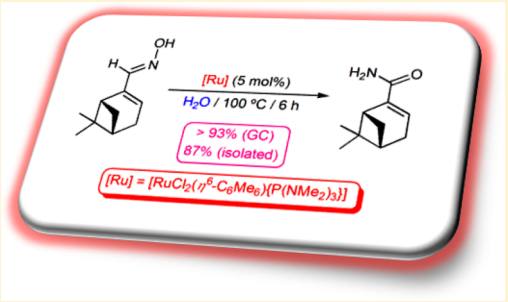
Rocío García-Álvarez,[†] Alba E. Díaz-Álvarez,[†] Javier Borge,[‡] Pascale Crochet,*[,†] and Victorio Cadierno*[,†]

[†]Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles", Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain

[‡]Departamento de Química Física y Analítica, Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain

Supporting Information

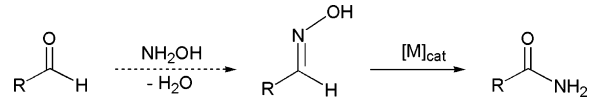
ABSTRACT: The rearrangement of aldoximes to primary amides has been studied using the readily available arene-ruthenium(II) complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (5 mol %) as catalyst. Reactions proceeded cleanly in pure water at 100 °C without the assistance of any cocatalyst, affording the desired amides in high yields (70−90%) after short reaction times (1−7 h). The process was operative with both aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldoximes and tolerated several functional groups. Reaction profiles and experiments using ^{18}O-labeled water indicate that two different mechanisms are implicated in these transformations. In both of them, nitrile intermediates are initially formed by dehydration of the aldoximes. These intermediates are then hydrated to the corresponding amides by the action of a second molecule of aldoxime or water. A kinetic analysis of the rearrangement of benzaldoxime to benzamide is also discussed.



INTRODUCTION

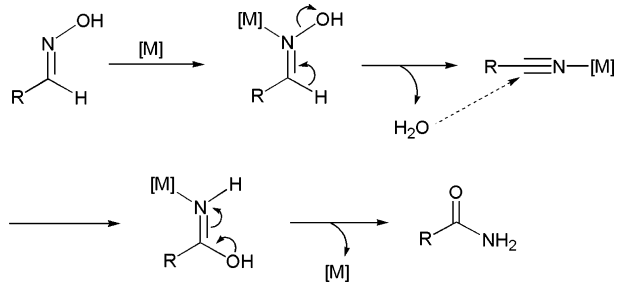
Amides are one of the most important functional groups in nature, constitute versatile building blocks in synthetic organic chemistry, and also exhibit a wide range of industrial applications and pharmacological interest.[1] Most syntheses of amides are based on the reaction of carboxylic acids and derivatives (halides, anhydrides, or esters) with amines.[1,2] However, these methods present several drawbacks, such as the use of toxic, corrosive, and/or expensive materials, highly exothermic reactions, low tolerance to sensitive functional groups, complex reaction conditions, and wasteful procedures. As a matter of fact, in 2005, the ACS GCIPR (American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable) identified amide formation as one of the most problematic syntheses in the pharmaceutical industry and labeled it as a high-priority research field.[3,4] Hence, the development of atom-efficient catalytic methods for amide formation has turned into a prime goal in modern chemistry.[5] In this context, the metal-catalyzed rearrangement of aldoximes, a process closely related to the well-known Beckmann rearrangement of ketoximes,[6] has emerged in recent years as an appealing tool for the generation of primary amides (Scheme 1).[5,7] Several Ni-, Pd-, Cu-, Au-, Ru-, Rh-, Ir-, Zn-, and In-based systems able to promote this atom-economical transformation are presently known.[8] In addition, examples allowing amide formation starting directly from aldehydes have also been described by performing the catalytic reactions in the presence of hydroxylamine, via *in situ* generation of the corresponding aldoxime intermediates.[8f,h,i,k,p,n,u,9,10]

Scheme 1. Metal-Catalyzed Rearrangement of Aldoximes to Amides



From a mechanistic point of view, two different reaction pathways have been proposed for this metal-catalyzed rearrangement. The first one involves the initial dehydration of the aldoxime into a nitrile intermediate, which is subsequently hydrated by the water released in the previous step to generate the final amide (Scheme 2). Both individual

Scheme 2. Catalytic Rearrangement of Aldoximes to Amides: The Classical Dehydration/Rehydration Mechanism



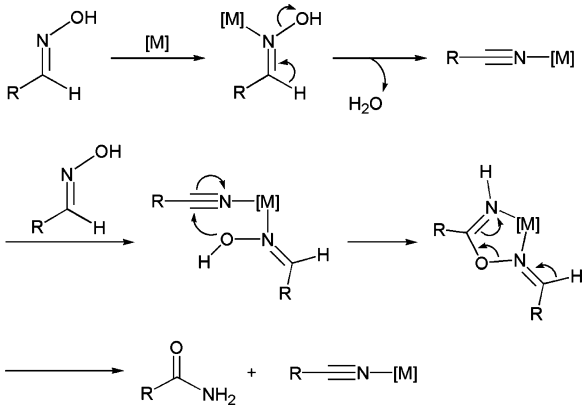
Received: July 23, 2012
Published: August 27, 2012

dx.doi.org/10.1021/om3006917 | *Organometallics* 2012, 31, 6482−6490

steps are promoted by the metal and have been independently reported in the literature with a broad range of metal catalysts.[11,12] The operativity of this mechanism was usually supported by the detection of small amounts of nitrile byproduct at the end of the catalytic reactions and, in one case, by their formation in the early stages before subsequent formation of the corresponding amides.[8h,i]

The second proposed mechanism involves again the initial metal-promoted dehydration of the aldoxime to form the corresponding nitrile, which now evolves into the final amide by the aid a second molecule of aldoxime, which acts as a water surrogate (Scheme 3).[13] Thus, intramolecular attack on the

Scheme 3. Catalytic Rearrangement of Aldoximes to Amides: Aldoximes As Water Surrogates



nitrile by a coordinated aldoxime leads to a five-membered cyclic intermediate, which decomposes into the final amide product and another coordinated nitrile, which continues with the catalytic cycle.[8l,m] Remarkably, despite that the dehydration/rehydration pathway involving water (Scheme 2) has been the generally accepted mechanism for the rearrangement of aldoximes to amides, a recent study by Williams and co-workers using ^{18}O-labeled substrates has pointed out that most of the metal catalysts described so far in the literature for this reaction really operate through the pathway depicted in Scheme 3.[8t]

During the last years, in the context of our studies on metal-catalyzed reactions in water,[14] we have developed a large number of hydrophilic ruthenium complexes able to promote efficiently the selective hydration of nitriles to primary amides in pure aqueous medium under neutral conditions.[15] Among them, best results in terms of activity were obtained with the arene-ruthenium(II) derivative $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$, which contains the commercially available and inexpensive P-donor ligand tris(dimethylamino)phosphine (Figure 1).[15e,f] The effectiveness of this readily accessible complex is ascribed to the excellent hydrogen bond accepting

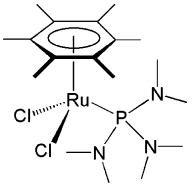


Figure 1. Structure of the arene-ruthenium(II) catalyst employed in this work.

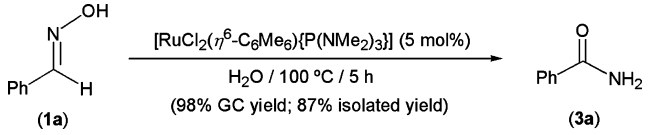
properties of $P(NMe_2)_3$, which activates the water molecule by H-bonding, thus enhancing its nucleophilic character.[16]

Herein, as a continuation of our work,[15e,f] the utility of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ for the catalytic rearrangement of aldoximes to primary amides in water is presented, along with evidence supporting that both mechanisms depicted in Schemes 2 and 3 are in this case operative. It is worthy of note that, despite the increasing interest in the use of environmentally friendly water as solvent for synthetic organic chemistry,[17,18] efforts devoted to develop such a catalytic rearrangement in water have been scarce. In fact, to the best of our knowledge, only one previous example involving the heterogeneous system $Rh(OH)_x/Al_2O_3$ has been quoted in the literature.[8h,i,19] A classical dehydration/rehydration mechanism of action, in which the nitrile intermediates are hydrated by water, was proposed for this heterogeneous system on the basis of reaction profiles.

RESULTS AND DISCUSSION

Catalytic Activity and Scope of Complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$. First, the ability of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ to promote the catalytic rearrangement of aldoximes was evaluated employing commercially available (*E*)-benzaldoxime (**1a**) as model substrate (Scheme 4). In this

Scheme 4. Ruthenium-Catalyzed Rearrangement of Benzaldoxime (1a) to Benzamide (3a) in Water



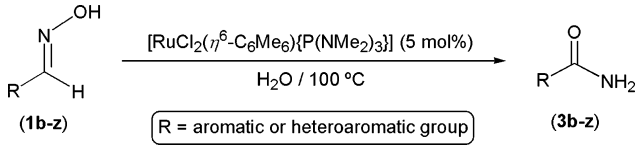
sense, we were pleased to find that, under the same experimental conditions previously employed in our nitrile hydration studies (0.33 M solution of the substrate in water, 5 mol % of Ru, 100 °C),[15e,f] the reaction proceeded efficiently to afford the desired benzamide (**3a**) in 98% GC yield after 5 h of heating. Complete consumption of **1a** along with the formation of a very minor amount of benzonitrile (**2a**; ca. 2%) as the only byproduct was observed by gas chromatography (GC). Solvent removal and subsequent chromatographic workup provided analytically pure benzamide in 87% isolated yield (details are given in the Experimental Section). It is important to note that, contrary to other catalytic systems previously described in the literature, no acidic cocatalysts were needed.[8g,l] In addition, compared with the aqueous $Rh(OH)_x/Al_2O_3$ heterogeneous system developed by Mizuno and co-workers,[8h,i] complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ was more active since a higher temperature (160 °C) and a longer reaction time (7 h) were required with $Rh(OH)_x/Al_2O_3$ (4 mol % of Rh) to generate **3a** in high yield (76%). Complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ proved also more effective than the related hydration catalysts $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$ (PTA-Bn = 1-benzyl-3,5-diaza-1-azonia-7-phosphatricyclo[3.3.1.1^{3,7}]decane chloride)[15a] and $[RuCl_2(\eta^3\text{:}\eta^3\text{-}C_{10}H_{16})(THPA)]$ ($C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl; THPA = 2,4,10-trimethyl-1,2,4,5,7,10-hexaaza-3-phosphatricyclo[3.3.1.1^{3,7}]decane)[15b] previously developed by us (under the same experimental conditions they led to benzamide in 76% and 60% GC yield, respectively, after 5 h of heating).[20]

Encouraged by this result, the scope of the process was next explored by carrying out the rearrangement of differently

dx.doi.org/10.1021/om3006917 | Organometallics 2012, 31, 6482−6490

substituted benzaldoximes **1b–u** (Table 1).[21] As observed for **1a**, all of them could be transformed into the corresponding

Table 1. Ruthenium-Catalyzed Rearrangement of Aromatic and Heteroaromatic Aldoximes in Water[a]



entry	aldoxime **1**	time (h)	yield (%) of **3**[b]
1	R = 2-F-C_6H_4 (**1b**)	5	**3b**; 91 (84)
2	R = 4-F-C_6H_4 (**1c**)	5	**3c**; 92 (86)
3	R = 2-Cl-C_6H_4 (**1d**)	5	**3d**; 80 (71)
4	R = 3-Cl-C_6H_4 (**1e**)	1	**3e**; 98 (84)
5	R = 4-Cl-C_6H_4 (**1f**)	2	**3f**; 94 (82)
6	R = 2,4-Cl_2-C_6H_3 (**1g**)	5	**3g**; 81 (69)
7	R = 2,6-Cl_2-C_6H_3 (**1h**)	5	**3h**; 96 (83)
8	R = 2-Cl-6-F-C_6H_3 (**1i**)	3	**3i**; 95 (84)
9	R = 3,5-Br_2-4-OH-C_6H_2 (**1j**)	7	**3j**; 96 (88)
10	R = C_6F_5 (**1k**)	1	**3k**; > 99 (93)
11	R = 2-NO_2-C_6H_4 (**1l**)	7	**3l**; 82 (75)
12	R = 4-NO_2-C_6H_4 (**1m**)	2	**3m**; 99 (91)
13	R = 2-Me-C_6H_4 (**1n**)	7	**3n**; 97 (87)
14	R = 3-Me-C_6H_4 (**1o**)	3	**3o**; 95 (88)
15	R = 4-Me-C_6H_4 (**1p**)	2	**3p**; 95 (86)
16	R = 2-OMe-C_6H_4 (**1q**)	24	**3q**; 74 (60)
17	R = 4-OMe-C_6H_4 (**1r**)	5	**3r**; 83 (72)
18	R = 4-OCF_3–C_6H_4 (**1s**)	5	**3s**; 99 (88)
19	R = 4-NH_2-C_6H_4 (**1t**)	7	**3t**; 95 (84)
20	R = 4-SMe-C_6H_4 (**1u**)	3	**3u**; 85 (76)
21	R = 2-naphthyl (**1v**)	5	**3v**; 93 (80)
22	R = 9-anthracenyl (**1w**)	7	**3w**; 94 (85)
23	R = 3-pyridyl (**1x**)	7	**3x**; 94 (82)
24	R = 5-Me-2-furyl (**1y**)	1	**3y**; 99 (90)
25	R = 2-thienyl (**1z**)	2	**3z**; 97 (86)

[a]Reactions performed under N_2 atmosphere at 100 °C using 1 mmol of the corresponding aldoxime (0.33 M in water). Substrate/Ru ratio: 100/5. [b]Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate chromatographic workup are given in parentheses.

primary amides **3b–u** in high yields (≥80% by GC; ≥71% after chromatographic purification; entries 1–20) after only 1–7 h of heating, regardless of their substitution pattern and electronic nature. However, due probably to steric factors, *ortho*-substituted substrates showed a lower reactivity compared to their *meta*- or *para*-substituted counterparts (e.g., entry 3 vs 4, 5; entry 11 vs 12; entry 13 vs 14, 15; or entry 16 vs 17). Remarkably, the present catalytic system tolerates different functional groups, such as halides (entries 1–10) or hydroxy (entry 9), nitro (entries 11–12), ethers (entries 16–18), amino (entry 19), or thioether (entry 20) functionalities, the latter being worthy of note since sulfur species are well-known poisons for homogeneous catalysts due to the formation of strong metal–sulfur bonds.[22] Polyaromatic substrates, such as naphthyl-2-carboxaldoxime (**1v**) and anthracenyl-9-carboxaldoxime (**1w**), as well as the heteroaromatic ones **1x–z**, containing pyridyl, furyl, and thienyl units, also participated in this reaction, delivering the desired primary amides **3v–z** in high yields after 1–7 h (≥93% by GC; ≥80% after chromatographic purification; entries 21–25 in Table 1). As in the case of **1a**, in all the reactions collected in Table 1, total consumption of the starting aldoximes was observed by GC and the only byproducts detected were the corresponding organonitriles RC≡N (**2b–z**).

At this point, we must note that despite the high generality shown by complex [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] for the catalytic rearrangement of aromatic and heteroaromatic aldoximes, it was completely inoperative when salicylaldoxime (**1aa**) and pyridine-2-carboxaldoxime (**1ab**) were used as substrates (Figure 2). In both cases, the starting material was

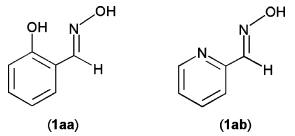
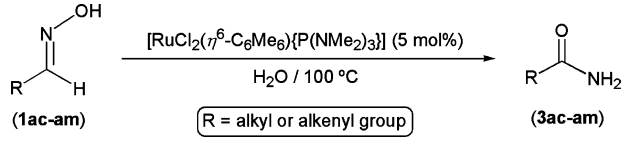


Figure 2. Structure of the unreactive aldoximes **1aa** and **1ab**.

recovered intact after 24 h of heating. These negative results could be explained by the high tendency of **1aa** and **1ab** to form stable six- and five-membered metallacycles, respectively, with metal ions.[23] Such a chelating *N,O*- or *N,N*-coordination of the aldoximes could block the ruthenium catalyst, thus preventing their rearrangement into the corresponding amides. This effect may also be responsible for the low reactivity observed with 2-methoxybenzaldoxime (**1q**), which required a long reaction period (24 h) to generate 2-methoxybenzamide (**3q**) in only 74% GC yield (Table 1; entry 16). On the other hand, intramolecular hydrogen bonds can also be established within **1aa** and **1ab** (particularly for its *Z* isomer), which may alternatively explain the lack of reactivity observed.

As shown in Table 2, complex [$RuCl_2(\eta^6$-$C_6Me_6)\{P(NMe_2)_3\}$] was also effective in the rearrangement of a variety of aliphatic and α,β-unsaturated aldoximes, thus confirming the wide scope of this catalytic transformation. Again, reactions proceeded in the absence of any additive. Thus, under the

Table 2. Ruthenium-Catalyzed Rearrangement of Aliphatic and α,β-Unsaturated Aldoximes in Water[a]



entry	aldoxime **1**	time (h)	yield (%) of **3**[b]
1	R = Me (**1ac**)	7	**3ac**; 99 (92)
2	R = Et (**1ad**)	3	**3ad**; 98 (90)
3	R = *n*-C_5H_{11} (**1ae**)	1	**3ae**; 96 (84)
4	R = *n*-C_6H_{13} (**1af**)	3	**3af**; 97 (88)
5	R = Cy (**1ag**)	3	**3ag**; 97 (89)
6	R = CH_2CH_2Ph (**1ah**)	1	**3ah**; 98 (86)
7	R = CH_2CH_2OPh (**1ai**)	2	**3ai**; 96 (87)
8	R = (*E*)-CH=CHPh (**1aj**)	1	**3aj**; 99 (88)
9	R = (*E*)-CH=CH-4–Cl-C_6H_4 (**1ak**)	2	**3ak**; 98 (89)
10	R = (*E*)-CH=CH-2-OMe-C_6H_4 (**1al**)	2	**3al**; 98 (91)
11	R = (*E*)-CH=CH-4-OMe-C_6H_4 (**1am**)	2	**3am**; 87 (79)

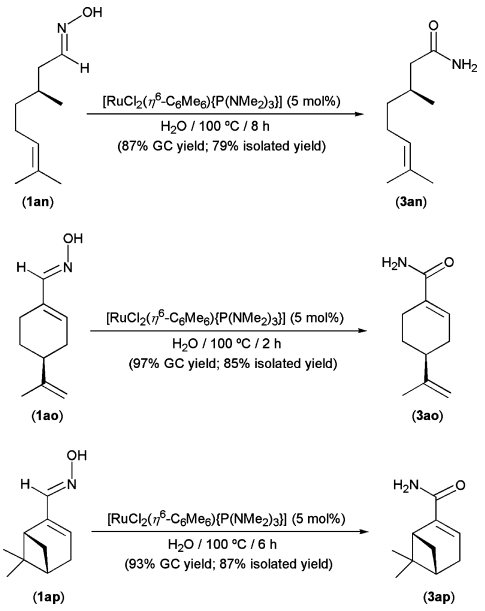
[a]Reactions performed under N_2 atmosphere at 100 °C using 1 mmol of the corresponding aldoxime (0.33 M in water). Substrate/Ru ratio: 100/5. [b]Yields determined by GC (uncorrected GC areas). Isolated yields after appropriate chromatographic workup are given in parentheses.

dx.doi.org/10.1021/om3006917 | *Organometallics* 2012, 31, 6482–6490

standard reaction conditions (5 mol % of Ru, 100 °C), aldoximes **1ac−am** were readily converted into the corresponding amides **3ac−am** with high yields and selectivities (87−99%). As in the precedent cases, formation of minor amounts of the respective nitriles **2ac−am** was also observed by GC.

Finally, the synthetic utility of the present method was further demonstrated in the preparation of the chiral amides **3an−ap** (Scheme 5). To our delight, they were cleanly

Scheme 5. Ruthenium-Catalyzed Rearrangement of Optically Active Aldoximes 1an−ap in Water



generated (79−87% isolated yields) by rearrangement of the known optically pure aldoximes **1an−ap**, derived from the naturally occurring aldehydes (*S*)-(−)-citronellal, (*S*)-(−)-perillaldehyde, and (1*R*)-(−)-myrtenal, respectively. The high-yield formation of the fragrance citronellamide (**3an**) (79%) merits highlighting since previous studies in organic media using nickel acetate as catalyst,[7c] or an excess of Raney Ni,[24] led to lower conversions (50−62%).[25] It is also worthy of note that, to the best of our knowledge, the catalytic transformations of **1ao-ap** to **3ao-ap** are unprecedented.[26,27]

Some Mechanistic Aspects. Once the scope of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ was demonstrated, we became interested in the elucidation of its mechanism of action. In this sense, the monitoring of the catalytic reactions by GC showed, in all the cases, that the starting aldoximes are readily consumed in the early stages of the catalytic events, generating a mixture of the corresponding nitriles and the final amides. As a representative example, the product distribution as a function of time for the ruthenium-catalyzed rearrangement of benzaldoxime (**1a**) to benzamide (**3a**) at 100 °C (Scheme 4) is given in Figure 3. As shown in the graphic, **1a** is totally consumed after 15 min of heating, with benzonitrile (**2a**; ca. 23%) and the final benzamide (**3a**; ca. 77%) being the only organic products present in solution. So, hydration of benzonitrile by the aid of benzaldoxime can be discarded from that moment, and only a classical hydration pathway by the water molecules present in the medium can be evoked (Scheme 2). However, we must note that, once the starting benzaldoxime has been consumed, conversion of benzonitrile into benzamide is a much slower

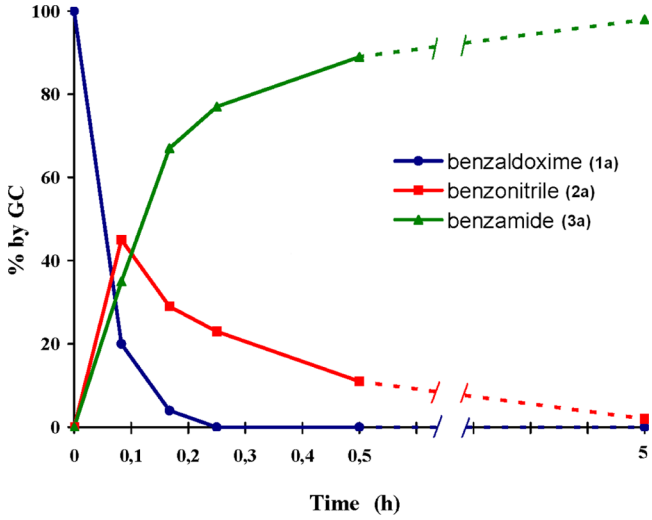


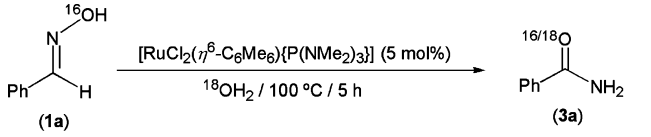
Figure 3. Product distribution as a function of time for the ruthenium-catalyzed rearrangement of benzaldoxime (**1a**) to benzamide (**3a**) at 100 °C in water (see Scheme 4).

process (additional 4.75 h are needed to completely hydrate the remaining 23% of **2a**).

The high initial reaction rate observed when benzaldoxime is still present in solution seems to indicate that the Williams mechanism depicted in Scheme 3 is probably operative at the beginning of the reaction. In line with this, when the catalytic rearrangement of benzaldoxime (**1a**) was carried out in organic media (anhydrous toluene or 1,2-dichloroethane) under the same experimental conditions (5 mol % of Ru; 100 °C), the process was also operative although less effective. Thus, 61−66% of benzamide (**2a**) was detected by GC in the crude reaction mixtures after 24 h of heating (to be compared with the data given in Scheme 4). As in the case of water, rapid dehydration of **1a** into **2a** also occurs (10−15 min) in toluene and 1,2-dichloroethane. At that time, the amount of benzamide (**3a**) formed is already 47−53% by GC, pointing out again remarkable rate differences in the presence or absence of benzaldoxime (**1a**). In addition, it seems also that the stoichiometric amount of water released during the dehydration of **1a** is not sufficient for completion of the subsequent rehydration step.

The catalytic rearrangement of **1a** in 97% ^{18}O-labeled water was also performed (Scheme 6). Analysis of the resulting

Scheme 6. Catalytic Rearrangement of Benzaldoxime (1a) to Benzamide (3a) in ^{18}O-Labeled Water



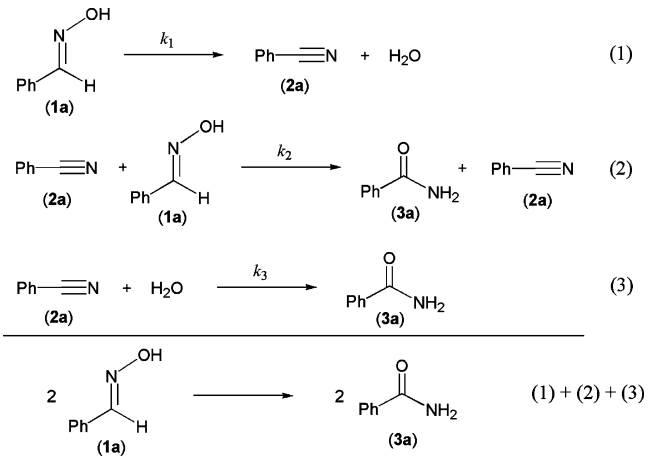
reaction product by high-resolution mass spectrometry (HRMS) showed the presence of both nonlabeled (m/z = 121.0551) and ^{18}O-labeled (m/z = 123.0574) benzamide in ca. 5.6:1 ratio (copies of the spectra of this sample and that generated from the reaction given in Scheme 4 are included in the Supporting Information). Incorporation of ^{18}O in the final benzamide clearly indicates that water molecules from the

dx.doi.org/10.1021/om3006917 | *Organometallics* 2012, 31, 6482−6490

solvent are to some extent participating in the reaction. However, the low ^{18}O-incorporation (ca. 15%) suggests that the classical dehydration/rehydration mechanism involving water (Scheme 2) is not the preferred pathway. The major formation of nonlabeled benzamide strongly supports the Williams mechanism as the main and faster path for the reaction in the early stages, in accord with the profile given in Figure 3.

Kinetic Analysis. In order to gain more information on these catalytic reactions, a kinetic analysis of the rearrangement of benzaldoxime (**1a**) to benzamide (**3a**) was performed. The proposed mechanisms for the rearrangement of aldoximes consist of several different chemical species and elementary reactions (see Schemes 2 and 3). Generally speaking, once a reaction mechanism has been established, it is possible to write the corresponding kinetic equations, to obtain therefrom a system of ordinary differential equations and to find, by means of a numerical method, the finest values of the rate constants of all the elementary steps. However, in our case, we can record experimental data (GC yields vs time) for only three compounds: benzaldoxime (**1a**), benzonitrile (**2a**), and benzamide (**3a**). Therefore, it is impossible to deal with the kinetic problem as conceived. Fortunately, a mechanism can be substituted by a "model" without losing its essential characteristics. The goal of this model is not to represent the whole chemistry of the process, but create a system of ordinary differential equations (easy to solve) that keep the essence of the original process. In this sense, as outlined in Scheme 7, a

Scheme 7. Adopted Model to Explain the Rearrangement of Benzaldoxime into Benzamide



very simple and intuitive model (3 steps and 3 independent chemical species; solvent is excluded) can be adopted to rationalize the overall rearrangement of benzaldoxime (**1a**) to benzamide (**3a**). It includes (i) the initial dehydration of **1a** into benzonitrile (**2a**), a common step in both mechanisms depicted in Schemes 2 and 3; (ii) the rehydration of **2a** by the aid of a second molecule of **1a**, step characteristic of the Williams mechanism (Scheme 3); and (iii) the classical hydration of **2a** by means of a water molecule to generate **3a**.

The sum of these three independent processes perfectly accounts for the observed rearrangement. Thus, while steps 1 and 2 represent the Williams mechanism (Scheme 3), steps 1 and 3 represent the classical one involving hydration of the nitrile by means of a water molecule (Scheme 2). Note that all steps in this model are assumed to be irreversible. Although this drastic reduction greatly simplifies the mathematical treatment, it is impossible to tackle, with guarantees of success, the resolution of the problem since the numerical methods that will be applied require, as usual, that the number of independent data is much higher than the number of unknowns (the rate constants k_1, k_2, and k_3 and the partial orders). As the disappearance of benzaldoxime (**1a**) takes place rapidly at 100 °C (see Figure 3), we decided to diminish the working temperature. At T = 60 °C the reaction rate slows down enough to get an appropriate set of experimental data, and thus the kinetic analysis was performed at this working temperature.[20] The analysis of the variation of the concentration of **1a** as a function of time (from 0 to 50 min; for t > 50 min, [**1a**] = 0 mol dm^{-3}) shows that the process follows a pseudo-first-order kinetics (linear correlation coefficient r = −0.9806). Also, using only the last six data points (from 60 to 1440 min; **1a** is already completely consumed) it can be assured that the hydration of benzonitrile (**2a**) into benzamide (**3a**) by means of a water molecule (Scheme 7, step 3) follows a pseudo-second-order kinetics (r = 0.9990) with respect to **2a**.[28] Combining all this information, it is possible to put forward the following system of three ordinary differential equations:

$$\frac{d[\mathbf{1a}]}{dt} = -k_1[\mathbf{1a}] - k_2[\mathbf{1a}] \quad (4)$$

$$\frac{d[\mathbf{2a}]}{dt} = +k_1[\mathbf{1a}] - k_3[\mathbf{2a}]^2 \quad (5)$$

$$\frac{d[\mathbf{3a}]}{dt} = +k_2[\mathbf{1a}] + k_3[\mathbf{2a}]^2 \quad (6)$$

The application of the "concentration−time integrals" (CTI)[29] method allows, on one hand, to obtain the values of the three rate constants and, on the other hand, to check the validity of the proposed model. The values of the rate constants obtained by the CTI method are dependent on the mathematical function chosen to fit the experimental data. In order to remove this dependence, the results of the CTI method were optimized with the aid of a nonlinear least-squares (NLLS) algorithm. We carried out all the calculations using MATLAB R2012a. The optimized values of the rate constants (at T = 60 °C) are

$$k_1 = 0.0145\ \text{min}^{-1} \quad k_2 = 0.0562\ \text{min}^{-1}$$
$$k_3 = 0.0316\ \text{dm}^3\ \text{mol}^{-1}\ \text{min}^{-1} \quad (7)$$

Figure 4 shows that the agreement between the observed and calculated data is fully satisfactory. The sum of squares due to error (SSE) is only 1.8 × 10^{-3}. Calculated data were obtained by numerical integration (using the optimized values of the rate constants, eq 7) of the system of differential equations described by eqs 4−6.[30]

Starting from the values of the three rate constants it is possible to calculate the rates of the three steps of the proposed model ($v_1 = k_1[\mathbf{1a}]$, $v_2 = k_2[\mathbf{1a}]$, and $v_3 = k_3[\mathbf{2a}]^2$). The overall rates of the Williams ($v_1 + v_2$) and classic ($v_1 + v_3$) mechanisms are shown in Figure 5. It is clearly observed that, when benzaldoxime (**1a**) is still present in solution, the Williams mechanism is predominant, particularly at the initial stages of the catalytic reaction. Once **1a** is consumed, only the classic mechanism involving water operates at very slow rates. These facts are in complete accord with the experimental observations made at 100 °C (see Figure 3) and previously commented on.

dx.doi.org/10.1021/om3006917 | Organometallics 2012, 31, 6482−6490

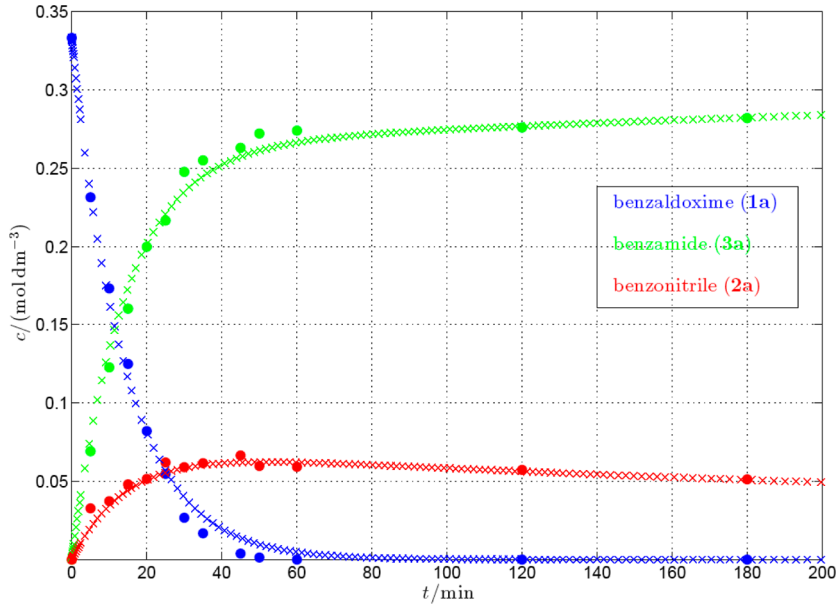


Figure 4. Experimental (filled circles) and calculated (cross) product distribution as a function of time for the ruthenium-catalyzed rearrangement of **1a** to **3a** at 60 °C in water.

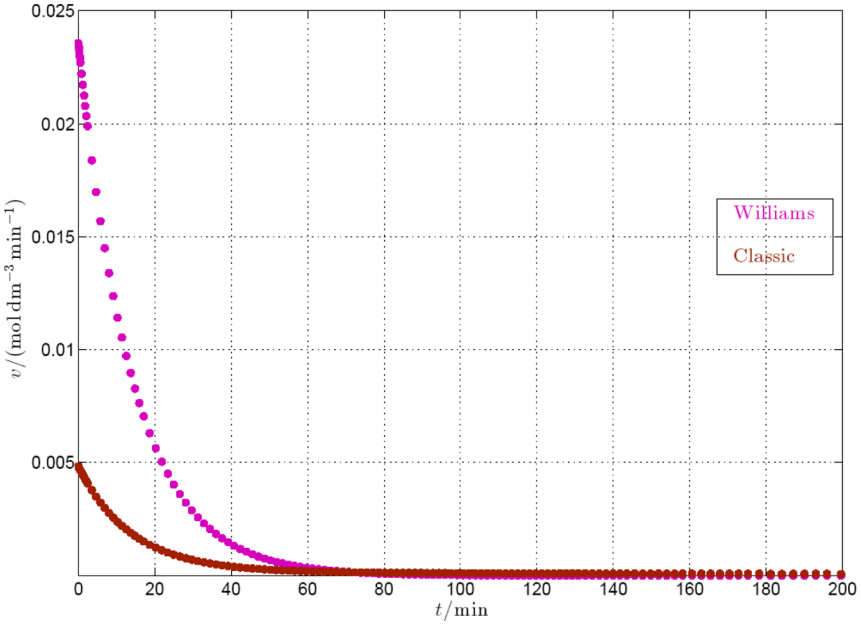


Figure 5. Overall rates (at T = 60 °C) of the Williams and classic mechanisms.

To further confirm the validity of the proposed kinetic model (eqs 4−6), we decided to apply it to the data set experimentally collected at T = 100 °C. Following the same mathematical procedure (CTI + NLLS) as above, the optimized values of the rate constants at this temperature are

$$k_1 = 0.2662\ \text{min}^{-1} \quad k_2 = 0.0641\ \text{min}^{-1}$$
$$k_3 = 0.9812\ \text{dm}^3\ \text{mol}^{-1}\ \text{min}^{-1} \qquad (8)$$

As expected, the values of the rate constants are all higher since the temperature has increased from 60 to 100 °C, with those of k_1 and k_3 showing a much higher increase in comparison with that of k_2.[31] The high quality of the fit (SSE = 5.9×10^{-4}) is shown in Figure 6.

CONCLUSION

In summary, we have developed a new protocol for the selective rearrangement of aldoximes to primary amides in a neutral aqueous medium, whose generality has been demonstrated for a huge range of substrates, including aromatic, heteroaromatic, α,β-unsaturated, and aliphatic ones. In addition, the high tolerance toward functional groups and the accessibility of complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$, which makes use of a commercially available and inexpensive phosphine ligand, confer this efficient synthetic approach of amides genuine potential for practical applications avoiding the use of classical organic solvents. It is also worthy of note that, from a mechanistic point of view, our work demonstrates for the first time that the two mechanisms proposed in the literature for this transformation are compatible for a single

dx.doi.org/10.1021/om3006917 | Organometallics 2012, 31, 6482−6490

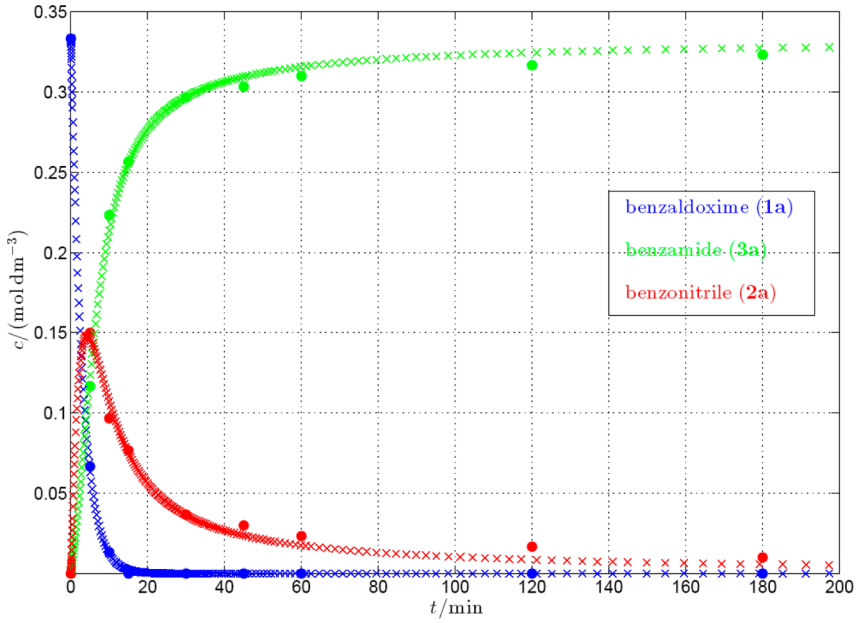


Figure 6. Experimental (filled circles) and calculated (cross) product distribution as a function of time for the ruthenium-catalyzed rearrangement of **1a** to **3a** at 100 °C in water.

catalyst, with that involving the hydration of the corresponding nitrile intermediates by a second molecule of aldoxime being predominant.

EXPERIMENTAL SECTION

GC measurements were performed on a Hewlett-Packard HP6890 equipment using a Supelco Beta-Dex 120 column (30 m length; 250 μm diameter). GC/MSD measurements were made with an Agilent 6890N equipment coupled to a 5973 mass detector (70 eV electron impact ionization) using a HP-1MS column. High-resolution mass spectra were provided by the mass spectrometry service of the University of Sevilla. Infrared spectra were recorded on a Perkin-Elmer 1720-XFT spectrometer. NMR spectra were recorded on a Bruker DPX-300 instrument at 300.1 MHz (^{1}H) or 75.47 MHz (^{13}C). The chemical shift values (δ) are given in parts per million and are referenced to the residual peak of the deuterated solvent used (CD_3OD). Elemental analyses were performed with a Perkin-Elmer 2400 microanalyzer. Optical rotations (α) at 20 °C at the sodium D-line were measured in a Perkin-Elmer 343 polarimeter. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). Complexes $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$,[15f] $[RuCl_2(\eta^6\text{-}C_6Me_6)(PTA\text{-}Bn)]$,[15a] and $[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(THPA)]$[15b] were prepared by following the methods previously reported by us.

General Procedure for the Synthesis of Aldoximes. Aldoximes **1b**−**1ap** (all of them known compounds) were synthesized by condensation of the corresponding aldehyde with $NH_2OH{\cdot}HCl$ as follows: To a solution of the appropriate aldehyde (40 mmol) in a mixture of methanol (20 mL) and pyridine (10 mL) was added hydroxylamine hydrochloride (4.5 g, 65 mmol), and the mixture stirred at room temperature for 24 h. Solvents were removed *in vacuo*, and the residual oil was extracted with diethyl ether (ca. 200 mL). The extract was then washed with water (3 × 15 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The crude product was purified by column chromatography over silica gel using diethyl ether/hexane (1:1) as eluent. The identity of aldoximes **1b**−**1ap**, which were in general obtained in 70−80% yield as mixtures of the corresponding *E* and *Z* isomers, was confirmed by mass spectrometry and ^{1}H and ^{13}C{^{1}H} NMR spectroscopy.

General Procedure for the Catalytic Rearrangement of Aldoximes. Under a nitrogen atmosphere, the corresponding aldoxime **1a**−**ap** (1 mmol), water (3 mL), and the ruthenium(II) catalyst $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (0.025 g, 0.05 mmol; 5 mol %) were introduced into a Teflon-capped sealed tube, and the reaction mixture was stirred at 100 °C for the indicated time (see Tables 1 and 2 and Schemes 4 and 5). The course of the reaction was monitored by regularly taking samples of ca. 20 μL, which after extraction with CH_2Cl_2 (3 mL) were analyzed by GC. After elimination of the solvent under reduced pressure, the crude reaction mixture was purified by column chromatography over silica gel using methanol/CH_2Cl_2 mixtures as eluent. In some cases, direct crystallization from the aqueous solution also allowed the isolation of pure products. The identity of the resulting primary amides was assessed by comparison of their ^{1}H and ^{13}C{^{1}H} NMR spectroscopic data with those reported in the literature and by their fragmentation in GC/MSD (copies of the ^{1}H and ^{13}C{^{1}H} NMR spectra of all the amides synthesized in this work (^{19}F NMR spectrum in the case of **3k**) are included in the Supporting Information). Characterization data for the novel amides **3ao** and **3ap** are as follows:

(*S*)-(−)-Perillamide (3ao): white solid. Yield: 85% (0.140 g). ^{1}H NMR (300.1 MHz, CD_3OD): δ 1.53 (m, 1H), 1.78 (s, 3H), 1.93 (m, 1H), 2.09−2.45 (m, 5H), 4.76 (s, 1H), 4.78 (s, 1H), 6.72 (br, 1H) ppm. NH_2 signals not observed. ^{13}C{^{1}H} NMR (75.47 MHz, CD_3OD): δ 19.5, 24.3, 27.0, 30.5, 40.1, 108.3, 132.2, 134.0, 148.8, 172.0 ppm. IR (KBr): ν 3350 (m), 3193 (w), 3079 (w), 2938 (m), 1660 (s), 1607 (s), 1521 (m), 1429 (m), 1367 (w), 1129 (w), 1043 (w), 943 (w), 923 (m), 883 (s), 723 (w), 637 (w), 477 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* 165 (20%, M$^+$), 137 (30), 122 (50), 107 (40), 91 (50), 67 (80), 44 (100), 27 (40). $[\alpha]^{20}_D$ = −111.8 (*c* = 0.03 M in MeOH). Anal. Calcd (%) for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.58; H, 9.23.

(1*R*)-(−)-Myrtenamide (3ap): white solid. Yield: 87% (0.144 g). ^{1}H NMR (300.1 MHz, CD_3OD): δ 0.85 (s, 3H), 1.15 (d, *J* = 8.3 Hz, 1H), 1.37 (s, 3H), 2.15 (br, 1H), 2.43−2.56 (m, 3H), 2.70 (m, 1H), 6.53 (br, 1H) ppm. NH_2 signals not observed. ^{13}C{^{1}H} NMR (75.47 MHz, CD_3OD): δ 19.9, 25.0, 30.8, 31.4, 37.3, 40.4, 41.5, 130.8, 142.8, 171.1 ppm. IR (KBr): ν 3392 (m), 3195 (w), 2918 (m), 1647 (s), 1601 (s), 1465 (w), 1404 (m), 1383 (w), 1331 (w), 1264 (w), 1109 (w), 1075 (w), 968 (w), 888 (m), 846 (w), 767 (m), 687 (w), 615 (w), 584 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* 165 (10%, M$^+$), 150 (10), 122 (80), 105 (90), 79 (100), 63 (30), 44 (90), 27 (40). $[\alpha]^{20}_D$ = −35.2 (*c* = 0.03 M in MeOH). Anal. Calcd (%) for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.75; H, 9.04.

dx.doi.org/10.1021/om3006917 | *Organometallics* 2012, 31, 6482−6490

■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of all the amides synthesized in this work (^{19}F NMR spectrum in the case of **3k**) and HRMS spectra of benzamide (**3a**) isolated from the reactions described in Schemes 4 and 6. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: crochetpascale@uniovi.es (P.C.); vcm@uniovi.es (V.C.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the Ministerio de Economía y Competitividad of Spain (Projects CTQ2010-14796/BQU and CSD2007-00006) is gratefully acknowledged.

■ REFERENCES

(1) See, for example: (a) *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, 1970. (b) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; Greenberg, A.; Breneman, C. M.; Liebman, J. F., Eds.; Wiley: New York, 2000. (c) *Polyesters and Polyamides*; Deopura, B. L.; Gupta, B.; Joshi, M.; Alagirusami, R., Eds.; CRC Press: Boca Raton, 2008. (d) Johansson, I. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley: New York, 2004; Vol. *2*, pp 442−463.

(2) See, for example: (a) Bailey, P. D.; Mills, T. J.; Pettecrew, R.; Price, R. A. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R.; Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; Vol. *5*, pp 201−294. (b) *Methoden Organic Chemistry (Houben Weyl)*; Dopp, D.; Dopp, H., Eds.; Thieme Verlag: Stuttgart, 1985; Vol. *E5*(2), pp 1024−1031.

(3) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zacks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411−420.

(4) A related industry-led survey highlighting the need for efficient amide formation methods can be found in: Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337−2347.

(5) For recent reviews covering innovative approaches for amide bond formation, see: (a) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405−3415. (b) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471−479.

(6) For reviews on the Beckmann rearrangement, see: (a) Kumar, R. R.; Vanithan, K. A.; Balasubramanian, M. In *Name Reactions for Homologations - Part 2*; Li, J. J., Ed.; John Wiley & Sons: Hoboken, NJ, 2009; pp 274−292. (b) Gawley, R. E. *Org. React.* **1988**, *35*, 1−420.

(7) Typically, the isomerization of aldoximes to primary amides has been performed using stoichiometric acidic reagents under harsh conditions. See, for example: (a) Horning, E. C.; Stromberg, V. L. *J. Am. Chem. Soc.* **1952**, *74*, 5151−5152. (b) Hoffenberg, D. S.; Hauser, C. R. *J. Org. Chem.* **1955**, *20*, 1496−1500. (c) Field, L.; Hughmark, P. B.; Shumaker, S. H.; Marshall, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 1983−1987.

(8) (a) Leusink, A. J.; Meerbeek, T. G.; Noltes, J. G. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 123−125. (b) Leusink, A. J.; Meerbeek, T. G.; Noltes, J. G. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 142−145. (c) Setsuda, T. Jpn. Kokai Tokkyo Koho JP 52128302, 1977. (d) Komiya, S.; Shimazu, H.; Tamashima, T. Jpn. Kokai Tokkyo Koho JP 2003342245, 2003. (e) Park, S.; Choi, Y.; Han, H.; Yang, S. H.; Chang, S. *Chem. Commun.* **2003**, 1936−1937. (f) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 73−75. (g) Oewston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 3599−3601. (h) Fujiwara, H.; Ogasawara, Y.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 5202−5205. (i) Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Yamaguchi, K.; Mizuno, N. *Chem. Asian J.* **2008**, *3*, 1715−1721. (j) Mishra, A.; Ali, A.; Upreti, S.; Gupta, R. *Inorg. Chem.* **2008**, *47*, 154−161. (k) Gnanamgari, D.; Crabtree, R. H. *Organometallics* **2009**, *28*, 922−924. (l) Kim, M.; Lee, J.; Lee, H.-Y.; Chang, S. *Adv. Synth. Catal.* **2009**, *351*, 1807−1812. (m) Allen, C. L.; Davulcu, S.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 5096−5099. (n) Allen, C. L.; Burel, C.; Williams, J. M. J. *Tetrahedron Lett.* **2010**, *51*, 2724−2726. (o) Ramón, R. S.; Bosson, J.; Díez-González, S.; Marion, N.; Nolan, S. P. *J. Org. Chem.* **2010**, *75*, 1197−1202. (p) Hull, J. F.; Hilton, S. T.; Crabtree, R. H. *Inorg. Chim. Acta* **2010**, *363*, 1243−1245. (q) Saidulu, G.; Anand, N.; Rao, K. S. R.; Burri, A.; Park, S.-E.; Burri, D. R. *Catal. Lett.* **2011**, *141*, 1865−1871. (r) Kumar, P.; Singh, A. K.; Pandey, R.; Pandey, D. S. *J. Organomet. Chem.* **2011**, *696*, 3454−3464. (s) Sharma, S. K.; Bishopp, S. D.; Allen, C. L.; Lawrence, R.; Bamford, M. J.; Lapkin, A. A.; Plucinski, P.; Watson, R. J.; Williams, J. M. J. *Tetrahedron Lett.* **2011**, *52*, 4252−4255. (t) Allen, C. L.; Lawrence, R.; Emmett, L.; Williams, J. M. J. *Adv. Synth. Catal.* **2011**, *353*, 3262−3268. (u) Martínez-Asensio, A.; Yus, M.; Ramón, D. J. *Tetrahedron* **2012**, *68*, 3948−3951.

(9) (a) Ali, M. A.; Punniyamurthy, T. *Adv. Synth. Catal.* **2010**, *352*, 288−292. (b) Gowda, R. R.; Chakraborty, D. *Eur. J. Org. Chem.* **2011**, 2226−2229. (c) Allam, B. K.; Singh, K. N. *Tetrahedron Lett.* **2011**, *52*, 5851−5854. (d) Raja, N.; Raja, M. U.; Ramesh, R. *Inorg. Chem. Commun.* **2012**, *19*, 51−54. (e) Prabhu, R. N.; Ramesh, R. *RSC Adv.* **2012**, *2*, 4515−4524.

(10) Note that the direct transformation of aldehydes to primary amides is especially exigent and usually requires the use of highly reactive reagents in excess quantities. See, for example: (a) Loupy, A.; Régnier, S. *Tetrahedron Lett.* **1999**, *40*, 6221−6224. (b) Sharghi, H.; Hosseini, M. *Synthesis* **2002**, 1057−1060. (c) Sharghi, H.; Sarvari, M. H. *Tetrahedron* **2002**, *58*, 10323−10328. (d) Ekoue-Kovi, K.; Wolf, C. *Chem.—Eur. J.* **2008**, *14*, 6302−6315 , and references therein.

(11) Examples of catalytic systems able to effect the selective dehydration of aldoximes to nitriles can be found in: (a) Attanasi, O.; Palma, P.; Serra-Zanetti, F. *Synthesis* **1983**, 741−742. (b) Hart-Davis, J.; Battioni, P.; Boucher, J.-L.; Mansuy, D. *J. Am. Chem. Soc.* **1998**, *120*, 12524−12530. (c) Yang, S. H.; Chang, S. *Org. Lett.* **2001**, *3*, 4209−4211. (d) Choi, E.; Lee, C.; Na, Y.; Chang, S. *Org. Lett.* **2002**, *4*, 2369−2371. (e) Ishihara, K.; Furuya, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2983−2986. (f) Yan, P.; Batamack, P.; Prakash, G. K. S.; Olah, G. A. *Catal. Lett.* **2005**, *101*, 141−143. (g) Yamaguchi, K.; Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3922−3925. (h) Kim, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 1717−1719. (i) Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2010**, *51*, 4479−4481. (j) Li, Y.-T.; Liao, B. S.; Chen, H.-P.; Liu, S.-T. *Synthesis* **2011**, 2639−2643.

(12) For reviews on metal-catalyzed nitrile hydration reactions, see: (a) Parkins, A. W. *Platinum Met. Rev.* **1996**, *40*, 169−174. (b) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771−1802. (c) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005**, *358*, 1−21. (d) Ahmed, T. J.; Knapp, S. M. M.; Tyler, D. R. *Coord. Chem. Rev.* **2011**, *255*, 949−974.

(13) Examples of catalytic hydrations of nitriles to amides using aldoximes as the water source have been described in: (a) Kim, E. S.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 2973−2975. (b) Lee, J.; Kim, M.; Chang, S.; Lee, H.-Y. *Org. Lett.* **2009**, *11*, 5598−5601. (c) Kim, E. S.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2010**, *51*, 1589−1591. (d) Kim, E. S.; Kim, Y. M.; Kim, J. N. *Bull. Korean Chem. Soc.* **2010**, *31*, 700−703. (e) Kiss, Á.; Hell, Z. *Tetrahedron Lett.* **2011**, *52*, 6021−6023. (f) Ma, X.-Y.; He, Y.; Hu, Y.-L.; Lu, M. *Tetrahedron Lett.* **2012**, *53*, 449−452. (g) Ma, X.; He, Y.; Wang, P.; Lu, M. *Appl. Organomet. Chem.* **2012**, *26*, 377−382.

(14) For selected recent examples, see: (a) Cadierno, V.; Francos, J.; Gimeno, J. *Green Chem.* **2010**, *12*, 135−143. (b) Lastra-Barreira, B.; Crochet, P. *Green Chem.* **2010**, *12*, 1311−1314. (c) Francos, J.; Cadierno, V. *Green Chem.* **2010**, *12*, 1552−1555. (d) Cadierno, V.; Francos, J.; Gimeno, J. *Chem. Commun.* **2010**, *46*, 4175−4177.

(e) Lastra-Barreira, B.; Francos, J.; Crochet, P.; Cadierno, V. *Green Chem.* **2011**, *13*, 307−313. (f) Cadierno, V.; Francos, J.; Gimeno, J. *Organometallics* **2011**, *30*, 852−862. (g) Cadierno, V.; Francos, J.; García-Garrido, S. E.; Gimeno, J. *Green Chem. Lett. Rev.* **2011**, *4*, 55−61. (h) Varela-Álvarez, A.; Sordo, J. A.; Piedra, E.; Nebra, N.; Cadierno, V.; Gimeno, J. *Chem.—Eur. J.* **2011**, *17*, 10583−10599. (i) Tomás-Mendivil, E.; Díez, J.; Cadierno, V. *Catal. Sci. Technol.* **2011**, *1*, 1605−1615. (j) Tomás-Mendivil, E.; Toullec, P. Y.; Díez, J.; Conejero, S.; Michelet, V.; Cadierno, V. *Org. Lett.* **2012**, *14*, 2520−2523.

(15) (a) Cadierno, V.; Francos, J.; Gimeno, J. *Chem.—Eur. J.* **2008**, *14*, 6601−6605. (b) Cadierno, V.; Díez, J.; Francos, J.; Gimeno, J. *Chem.—Eur. J.* **2010**, *16*, 9808−9817. (c) García-Álvarez, R.; Díez, J.; Crochet, P.; Cadierno, V. *Organometallics* **2010**, *29*, 3955−3965. (d) García-Garrido, S. E.; Francos, J.; Cadierno, V.; Basset, J.-M.; Polshettiwar, V. *ChemSusChem* **2011**, *4*, 104−111. (e) García-Álvarez, R.; Francos, J.; Crochet, P.; Cadierno, V. *Tetrahedron Lett.* **2011**, *52*, 4218−4220. (f) García-Álvarez, R.; Díez, J.; Crochet, P.; Cadierno, V. *Organometallics* **2011**, *30*, 5442−5451. (g) García-Álvarez, R.; García-Garrido, S. E.; Díez, J.; Crochet, P.; Cadierno, V. *Eur. J. Inorg. Chem.* **2012**, in press (DOI: 10.1002/ejic.201200592).

(16) This property has been recently exploited by Tyler and co-workers in the challenging catalytic hydration of cyanohydrins to the corresponding α-hydroxyamides, where the related arene-Ru(II) complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(NMe_2)_3\}]$ showed an unprecedented reactivity: Knapp, S. M. M.; Sherbow, T. J.; Juliette, J. J.; Tyler, D. R. *Organometallics* **2012**, *31*, 2941−2944.

(17) For leading references in this field, see: (a) Li, C. J.; Chan, T. H. In *Comprehensive Organic Reactions in Aqueous Media*; John Wiley & Sons: NJ, 2007. (b) *Organic Reactions in Water: Principles, Strategies and Applications*; Lindstrom, U. M., Ed.; Blackwell Publishing Ltd.: Oxford, 2007. (c) *Aqueous-Phase Organometallic Catalysis: Concepts and Applications*; Cornils, B.; Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1998. (d) Joó, F. In *Aqueous Organometallic Catalysis*; Kluwer: Dordrecht, 2001.

(18) One of the crucial points in realizing a "green chemical" process involves the choice of a safe, nontoxic, and cheap solvent. In this context, water is the first solvent of choice regarding the aforementioned considerations: (a) Nelson, W. M. In *Green Solvents for Chemistry: Perspectives and Practice*; Oxford University Press: New York, 2003. (b) Clark, J. H.; Taverner, S. J. *Org. Process Res. Dev.* **2007**, *11*, 149−155. (c) Kerton, F. M. In *Alternative Solvents for Green Chemistry*; RSC Publishing: Cambridge, 2009.

(19) A limited number of examples of amide formation reactions starting directly from aldehydes and hydroxylamine (Scheme 1) in aqueous media have also been described. See refs 8u and 9a−c.

(20) (a) As expected, the use of lower temperatures and/or loadings of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ reduces the yield of **3a** and slows the reaction. For example, when using 5 mol % of Ru at 60 °C, 24 h were needed to produce **3a** in 94% GC yield (87% after 5 h), while the use of 2 mol % of Ru at 100 °C led to **3a** in only 82% yield after 24 h (74% after 5 h). (b) As observed in our previous nitrile hydration studies (ref 15f), complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ slowly decomposes under the catalytic reaction conditions to generate the inactive species $[RuCl_2(\eta^6\text{-}C_6Me_6)(NHMe_2)]$, via hydrolysis of the $P(NMe_2)_3$ ligand. On the other hand, a Brønsted acid catalysis has been discarded since only a minor amount of benzamide (ca. 15%) is formed using catalytic HCl (5 mol%) instead of $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ under the same reaction conditions.

(21) Most of the aldoximes employed in this work were synthesized as mixtures of the corresponding *E* and *Z* isomers in ratios ranging from 95:5 to 30:70. As previously observed in related works (see ref 8), no differences in reactivity between both stereoisomers were observed.

(22) (a) Dunleavy, J. *Platinum Met. Rev.* **2006**, *50*, 110. (b) For a recent example of the poisoning of a homogeneous ruthenium catalyst by the methylsulfanyl group, see: Díaz-Álvarez, A. E.; Crochet, P.; Cadierno, V. *Tetrahedron* **2012**, *68*, 2611−2620.

(23) Representative examples of stable metal complexes gerenated by chelation of **1aa** and **1ab** can be found in: (a) Hultgren, V. M.; Atkinson, I. M.; Beddoes, R. L.; Collison, D.; Garner, C. D.; Helliwell, M.; Lindoy, L. F.; Tasker, P. A. *Chem. Commun.* **2001**, 573−574. (b) Babu, M. S. S.; Krishna, P. G.; Reddy, K. H.; Philip, G. H. *J. Chil. Chem. Soc.* **2009**, *54*, 339−344. (c) Abu-Youssef, M. A. M.; Soliman, S. M.; Langer, V.; Gohar, Y. M.; Hasanen, A. A.; Makhyoun, M. A.; Zaky, A. H.; Öhrström, L. R. *Inorg. Chem.* **2010**, *49*, 9788−9797. (d) Zeheng, L.; Zhang, S.; Li, K.; Chen, W.; Chen, Y.; Xu, B.; Hu, B.; Li, Y.; Li, W. *J. Mol. Struct.* **2010**, *984*, 153−156. (e) Rusanova, J. A.; Buvaylo, E. A.; Rusanov, E. B. *Acta Crystallogr., Sect. E* **2011**, *E67*, m222−m223. (f) Konidaris, K. F.; Polyzou, C. D.; Kostakis, G. E.; Tasiopoulos, A. J.; Roubeau, O.; Teat, S. J.; Manessi-Zoupa, E.; Powell, A. K.; Perlepes, S. P. *Dalton Trans.* **2012**, *41*, 2862−2865.

(24) Caldwell, A. G.; Jones, E. R. H. *J. Chem. Soc.* **1946**, 599−601.

(25) Isomerization of **1an** into **3an** could be achieved in 85% yield by means of excess KOH at 180 °C under anhydrous conditions: Oku, M.; Fujikura, Y.; Etsuno, J. Jpn. Kokai Tokkyo Koho JP 07138213, 1995.

(26) Perillamide (**3ao**), which seems to possess interesting olfactory and antimicrobial properties, has been mentioned in a couple of patents. However, neither details on its synthesis nor characterization data were given in the documents: (a) Rieks, A.; Kähler, M.; Kirchner, U.; Wiggenhorn, K.; Kinzer, M.; Risch, S. PCT Int. Appl. WO 2004/076400, 2004. (b) Ray, A.; Boyle, S. M. PCT Int. Appl. WO 2011/130726, 2011.

(27) Myrtenamide (**3ap**) is a new compound that has not been previously described in the literature.

(28) In an independent experiment, the hydration of benzonitrile (**2a**) into benzamide (**3a**) in water (0.33 M) mediated by complex $[RuCl_2(\eta^6\text{-}C_6Me_6)\{P(NMe_2)_3\}]$ (0.5 mol%) was studied at $T = 60$ °C, and a pseudo-second-order kinetics with respect to **2a** was also found ($r = 0.9889$).

(29) (a) French, D. *J. Am. Chem. Soc.* **1950**, *72*, 4806−4807. (b) Saville, D. *J. Phys. Chem.* **1971**, *75*, 2215−2217.

(30) The selected routine for the numerical integration, *ode15s*, is a variable-order stiff solver based on numerical differentiation formulas. The relative and absolute error tolerances were set to 10^{-6} and 10^{-10}, respectively.

(31) This fact indicates that the classic mechanism (Scheme 2) is much more dependent on the temperature than the Williams one (Scheme 3). However, we must note that the accuracy of the calculated values of the rate constants in eq 8 is low (for $t > 15$ min, [**1a**] = 0 mol dm^{-3} at 100 °C). The remarkable increase of k_3 with temperature is not unexpected since harsh conditions are usually required in metal-catalyzed nitrile hydration processes (see ref 12).