



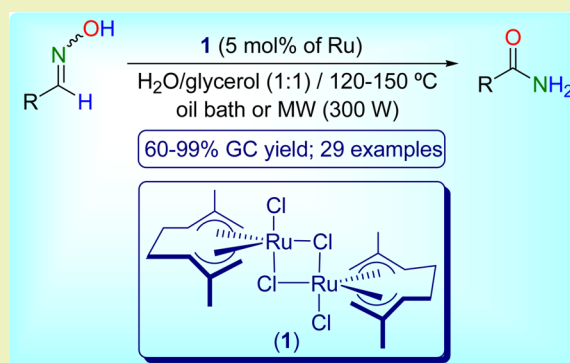
# Catalytic Rearrangement of Aldoximes to Primary Amides in Environmentally Friendly Media under Thermal and Microwave Heating: Another Application of the Bis(allyl)-Ruthenium(IV) Dimer $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$

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## Supporting Information

**ABSTRACT:** The rearrangement of aldoximes to primary amides has been studied using the commercially available bis(allyl)-ruthenium(IV) complex  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**;  $\text{C}_{10}\text{H}_{16}$  = 2,7-dimethylocta-2,6-diene-1,8-diyl) as a catalyst under thermal and microwave heating. The reactions proceeded cleanly in a mixture of water/glycerol (1:1) at 120–150 °C, without the assistance of any cocatalyst, affording the desired amides in moderate to high yields and short times. The process was operative with aromatic, heteroaromatic, aliphatic, and  $\alpha,\beta$ -unsaturated aldoximes and tolerated the presence of several functional groups in the substrates. In addition, the recyclability of catalyst **1** (up to six consecutive runs) could be demonstrated.



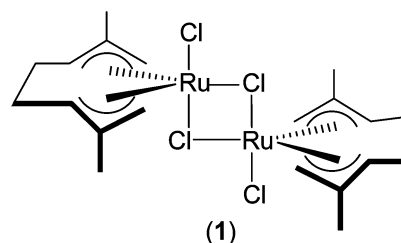
**KEYWORDS:** Rearrangement of aldoximes, Synthesis of amides, Green solvents, Ruthenium catalysts, Microwave heating

## INTRODUCTION

Sustainability represents nowadays one of the major focuses of attention within the scientific community.<sup>1,2</sup> Accordingly, chemical transformations are experiencing a deep change to meet sustainability criteria consistent with the green chemistry principles.<sup>3,4</sup> Among these principles, the choice of a safe, nontoxic, eco-friendly, and cheap solvent represents a crucial factor in realizing a “green” chemical process.<sup>5</sup> In this sense, water was early recognized as the most convenient candidate to replace undesired petroleum-based solvents, and consequently, the use of aqueous reaction media in synthetic chemistry has spread at a staggering pace during the past two decades.<sup>6–9</sup> More recently, glycerol has also emerged as an appealing alternative. Being the major byproduct in the production of biodiesel ( $\approx 10\%$  by weight), glycerol is nontoxic, nonflammable, biodegradable, and immiscible with hydrocarbons.<sup>10</sup> These properties, together with its economic attractiveness, make it an interesting reaction medium from both conceptual and environmental view points.<sup>11–17</sup> In addition, like water, the high polarity and dielectric constant of glycerol also make it a very suitable solvent for microwave-assisted reactions.<sup>18–21</sup> Note that the application of microwave irradiation (MW) in organic synthesis usually provides enhanced reaction rates and product yields in comparison to conventional thermal heating methodologies<sup>22–24</sup> and allows a reduction of the energetic

expenditure associated with the process,<sup>25</sup> an aspect that constitutes another spearhead of green chemistry.<sup>3,4</sup>

In this context, during the past few years, our research group has been deeply involved in the search of metal catalysts for synthetically useful organic transformations able to operate in these green reaction media. Among the systems developed, what stands out is the bis(allyl)-ruthenium(IV) complex  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  ( $\text{C}_{10}\text{H}_{16}$  = 2,7-dimethylocta-2,6-diene-1,8-diyl; **1**; see Figure 1), a commercially available compound (Strem Chemicals, Inc.) readily accessible by



**Figure 1.** Structure of the bis(allyl)-ruthenium(IV) complex  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**) employed in this work.

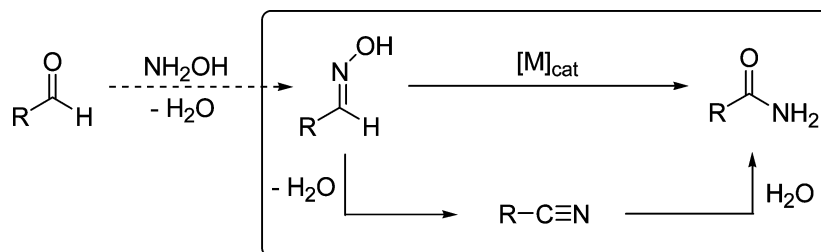
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Scheme 1. Metal-catalyzed Rearrangement of Aldoximes to Amides



treatment of ruthenium trichloride with isoprene.<sup>26</sup> When employing this air-stable organometallic complex, or its derivatives, efficient protocols for the isomerization of allylic-alcohols,<sup>27</sup> -ethers,<sup>28</sup> and -benzenes;<sup>29,30</sup> the deprotection of allylic-amines<sup>31</sup> and -amides;<sup>32</sup> the hydro-oxy-carbonylation of alkynes;<sup>33,34</sup> the hydration of nitriles;<sup>35,36</sup> the alkylation of indoles;<sup>37</sup> and the cyclotrimerization of alkynes<sup>38,39</sup> in water (or glycerol in some cases) could be developed. Interestingly, given the insolubility of  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**) in water, most of these catalytic transformations took place under heterogeneous or, in the case of liquid substrates immiscible with water, biphasic conditions, with greater effectiveness to those observed in the homogeneous phase employing classical organic solvents.

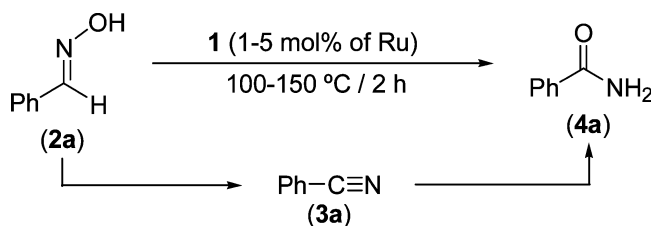
Following with these studies, we report herein a new synthetic application of complex  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**), i.e. its ability to promote the rearrangement of aldoximes (Scheme 1). Since aldoximes can be easily accessed from inexpensive aldehydes, this process, which involves a dehydration/rehydration sequence via the formation of a nitrile intermediate, has emerged in recent years as an attractive and atom-economical strategy for the preparation of primary amides.<sup>40–42</sup> It should be emphasized at this point that, “amide formation avoiding poor atom economic reagents” was identified by the ACS GCIPR (American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable) as one of the top challenges in current organic chemistry.<sup>43</sup>

Although several catalytic systems for this rearrangement process have already been described in the literature, the vast majority only operate in organic media,<sup>44</sup> and those active in water have drawbacks such as the use of expensive metals<sup>45,46</sup> or elaborated ligands,<sup>47</sup> limited substrate scope,<sup>48</sup> or poor recyclability.<sup>49,50</sup> As the reader will see, by using  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**) as catalyst, in a water/glycerol mixture as the reaction medium, these limitations could be now circumvented.

## RESULTS AND DISCUSSION

**Optimization of the Reaction Conditions.** Initially, in order to establish the optimal reaction conditions, we checked the behavior of dimer  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**) in the rearrangement of the commercially available (*E*)-benzaloxime (**2a**) as a model substrate (see Table 1). In this sense, different solvents, catalyst loadings, and temperatures were tested. Thus, we found that, when a 0.33 M solution of (*E*)-benzaloxime (**2a**) was heated in a sealed tube for 2 h at 100 °C with a catalytic amount of **1** (5 mol % of Ru), employing various conventional organic solvents, benzamide (**4a**) was formed in almost negligible GC yields (1–12%; see entries 1–4 in Table 1). However, by using water (entry 5) or glycerol (entry 6) as a solvent, the rate of the isomerization

**Table 1.** Rearrangement of (*E*)-Benzaloxime (**2a**) into Benzamide (**4a**) Catalyzed by the Bis(allyl)-Ru(IV) Complex **1**: Optimization of the Reaction Conditions<sup>a</sup>



entry	solvent	catalyst loading	temp. (°C)	conv. (%) <sup>b</sup>	yield (%) of <b>4a</b> <sup>b</sup>
1	acetonitrile	5 mol % Ru	100	21 (52)	1 (6)
2	THF	5 mol % Ru	100	57 (>99)	12 (37)
3	toluene	5 mol % Ru	100	50 (>99)	2 (25)
4	<sup>i</sup> PrOH	5 mol % Ru	100	43 (>99)	2 (10)
5	H <sub>2</sub> O	5 mol % Ru	100	> 99	42 (49)
6	glycerol	5 mol % Ru	100	> 99	40 (44)
7	H <sub>2</sub> O/glycerol (1:1)	5 mol % Ru	100	> 99	53 (61)
8	H <sub>2</sub> O/glycerol (1:1)	5 mol % Ru	120	> 99	62 (74)
9	H <sub>2</sub> O/glycerol (1:1)	5 mol % Ru	150	> 99	60 (74)
10	H <sub>2</sub> O/glycerol (1:1)	3 mol % Ru	120	81 (>99)	35 (47)
11	H <sub>2</sub> O/glycerol (1:1)	1 mol % Ru	120	52 (>99)	23 (28)

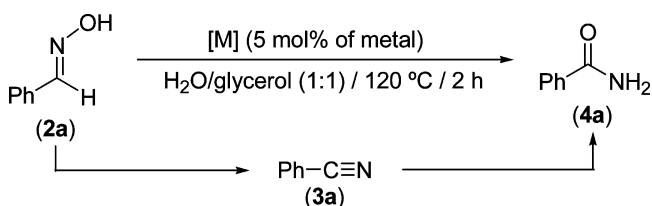
<sup>a</sup>All the reactions were performed in a Teflon-capped sealed tube under a N<sub>2</sub> atmosphere using 1 mmol of (*E*)-benzaloxime (**2a**) (0.33 M in the corresponding solvent). <sup>b</sup>Conversions and yields determined by GC after 2 h (conversions and yields after 24 h are given in parentheses). The differences between conversion and benzamide (**4a**) yield correspond to the intermediate benzonitrile (**3a**) present in the reaction media.

process could be significantly enhanced, leading to the formation of the desired benzamide (**4a**) in 40–42% GC yield after 2 h. In addition, a further improvement was achieved employing a mixture of water and glycerol (1:1) as a solvent (53% GC yield after 2 h; entry 7). On the other hand, we have also screened the optimal working temperature by performing experiments at 120 and 150 °C, and we observed that an improvement in the reaction rate occurs by increasing the temperature to 120 °C (62% GC yield after 2 h; entry 8). However, an additional increase of the temperature to 150 °C did not allow an improvement of the yield of benzamide (**4a**; 60% GC yield after 2 h; entry 9). As it was expected, a decrease in the catalyst loading from 5 mol % to 3 or 1 mol % of Ru is accompanied by a reduction in the efficiency of the process (35 and 23% GC yield of benzamide, respectively; see entries 10–11 in Table 1). Finally, it is also worthy of note that a variation

on the concentration of the substrate to 0.2 or 0.5 M did not significantly affect either the efficiency or selectivity of the process. In accord with all these results, a catalyst loading of 5 mol % of Ru, a mixture of water and glycerol (1:1) as a solvent, and a temperature of 120 °C were considered as the optimal reaction conditions for the rest of our catalytic studies. It is important to note at this point that, contrary to other catalytic systems previously described in the literature, no acidic cocatalysts were in this case needed.<sup>51–53</sup>

In order to determine the real potential of complex  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**) for this rearrangement process, the activity of several other commercially available metallic precursors was checked in the catalytic rearrangement of (*E*)-benzaloxime (**2a**; see Table 2). Thus, under the

**Table 2. Metal Catalyzed Rearrangement of (*E*)-Benzaloxime (**2a**) to Benzamide (**4a**) in a Mixture Water/Glycerol (1:1)<sup>a</sup>**



entry	catalyst precursor	conv. (%) <sup>b</sup>	yield (%) of <b>4a</b> <sup>b</sup>
1	$[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$ ( <b>1</b> )	> 99	62 (74)
2	$[\text{RuCl}_2(\eta^3\text{-}\eta^2\text{-}\eta^3\text{-C}_{12}\text{H}_{18})]$	> 99	53 (60)
3	$[\{\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-C}_6\text{Me}_6)\}_2]$	> 99	60 (71)
4	$[\{\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-mesitylene})\}_2]$	> 99	57 (70)
5	$[\{\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-}p\text{-cymene})\}_2]$	> 99	55 (66)
6	$[\{\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-C}_6\text{H}_6)\}_2]$	> 99	42 (51)
7	$[\text{RuCl}_2(\text{PPh}_3)_3]$	81 (>99)	32 (47)
8	$[\{\text{RuCl}_2(\text{cod})\}_n]$	52 (83)	12 (17)
9	$[\text{RuCl}(\eta^5\text{-C}_9\text{H}_7)(\text{PPh}_3)_2]$	31 (40)	7 (9)
10	$[\text{Ru}_3(\text{CO})_{12}]$	21 (25)	4 (6)
11	$[\{\text{Rh}(\mu\text{-Cl})(\text{cod})\}_2]$	10 (16)	2 (4)
12	$[\{\text{Rh}(\mu\text{-Cl})(\text{coe})_2\}_2]$	7 (11)	2 (3)
13	$[\{\text{Rh}(\mu\text{-Cl})(\text{nbd})\}_2]$	8 (14)	2 (4)
14	$[\{\text{Ir}(\mu\text{-Cl})(\text{cod})\}_2]$	7 (11)	2 (5)
15	$[\text{Pd}_2(\text{dba})_3]$	2 (8)	0 (3)
16	$\text{Pd}(\text{OAc})_2$	2 (9)	1 (4)
17	$\text{PtCl}_2$	8 (16)	3 (7)

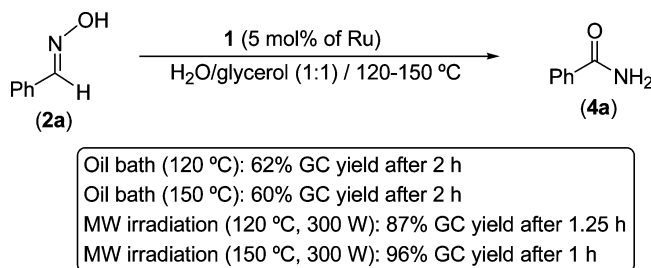
<sup>a</sup>All the reactions were performed in a Teflon-capped sealed tube under a N<sub>2</sub> atmosphere at 120 °C using 1 mmol of (*E*)-benzaloxime (**2a**) (0.33 M in a mixture water/glycerol (1:1)). Substrate/metal ratio: 100:5. <sup>b</sup>Conversions and yields determined by GC after 2 h (conversions and yields after 24 h are given in parentheses). The differences between conversion and benzamide (**4a**) yield correspond to the intermediate benzonitrile (**3a**) present in the reaction media.

optimized reaction conditions mentioned above, in addition to complex **1** (entry 1), only the related bis(allyl)-Ru(IV) derivative  $[\text{RuCl}_2(\eta^3\text{-}\eta^2\text{-}\eta^3\text{-C}_{12}\text{H}_{18})]$  ( $\text{C}_{12}\text{H}_{18}$  = dodeca-2,6,10-triene-1,12-diyl; entry 2) and the arene-Ru(II) dimers  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-arene})\}_2]$  (arene = C<sub>6</sub>Me<sub>6</sub>, mesitylene, *p*-cymene, C<sub>6</sub>H<sub>6</sub>; entries 3–6) afforded the desired benzamide (**4a**) as the major reaction product (≥51% GC yield after 24 h). The rest of the ruthenium precatalysts employed gave rise preferentially to the intermediate benzonitrile (**3a**; entries 7–10). Finally, the rhodium (entries 11–13), iridium (entry 14), palladium (entries 15–16), and platinum (entry 17) precursors tested

showed all almost negligible activity in the process, with only traces of benzamide (**4a**) being detected by GC after 24 h. From this general catalyst screening, ruthenium clearly emerged as the metal of choice, with the bis(allyl)-Ru(IV) dimer  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**) leading, under the experimental conditions employed, to the best results in terms of both activity and selectivity (62% GC yield after 2 h; entry 1).

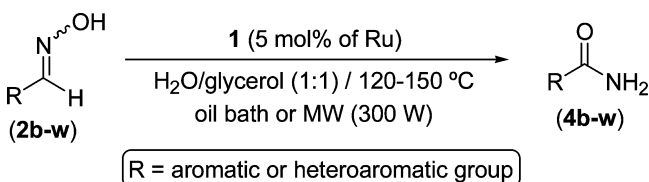
As it was previously commented, the application of microwave irradiation (MW) as a heating source in organic synthesis has become a very attractive alternative to the conventional heating methodologies.<sup>22–24</sup> Hence, aiming to enhance the catalytic activity of complex **1**, as well as to compare with the results obtained using oil bath heating, we decided to explore the behavior of **1** under microwave irradiation. Thus, taking again as a model reaction the rearrangement of (*E*)-benzaloxime (**2a**) into benzamide (**4a**) under our optimized reaction conditions (5 mol % of Ru, in a mixture water/glycerol (1:1) at 120 °C), a significant increase in the effectiveness of the process was observed using MWs as the heating source (300 W; 87% GC yield after 1.25 h vs 62% GC yield after 2 h; see Scheme 2). Moreover, contrary

**Scheme 2. Rearrangement of (*E*)-Benzaloxime (**2a**) into Benzamide (**4a**) Using Dimer **1**: Comparison between Thermal Heating and Microwave Irradiation**



to what was observed in the oil bath, a rise in the working temperature from 120 to 150 °C entailed in this case a noticeable increase in the catalytic activity, obtaining benzamide (**4a**) almost quantitatively in a short reaction time (96% GC yield after 1 h; see Scheme 2).

**Scope of the Reaction.** In order to investigate the scope of the process, the rearrangement of a series of differently substituted aromatic and heteroaromatic aldoximes **2b–2w** by complex  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**) was next explored under oil-bath heating and MW conditions (see Table 3). Most of these aldoximes were synthesized as mixtures of the corresponding *E* and *Z* isomers, in ratios ranging from 95:5 to 30:70, but no differences in reactivity between both stereoisomers were observed. As a general trend, the use of MW irradiation led to higher yields in the desired amides and shorter reaction times. Thus, similarly to the case of benzaloxime (**2a**), its substituted counterparts **2b–2q** were transformed into the corresponding benzamides **4b–4q** in high yields (≥86% by GC; ≥79% after chromatographic purification; entries 1–16) after only 0.5–2 h of irradiation, regardless of their substitution pattern or electronic nature. However, due probably to steric factors, *ortho*-substituted substrates showed a lower reactivity compared to their *meta*- or *para*-substituted analogues (e.g., entry 2 vs 3–4, entry 9 vs 10, or entry 11 vs 12–13). Polyaromatic substrates, such as naphthyl-2-carbaldoxime (**2r**) and anthracenyl-9-carbaldoxime (**2s**), as well as the heteroaromatic ones **2t–2w**, containing pyridyl, furyl, and

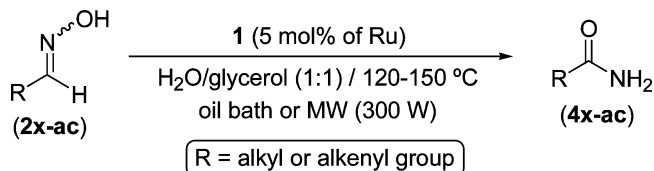
**Table 3.** Rearrangement of Various Aromatic and Heteroaromatic Aldoximes Catalyzed by the Bis(allyl)-Ru(IV) Complex **1** in a Mixture Water/Glycerol (1:1)<sup>a</sup>

entry	aldoxime <b>2</b> (R)	oil bath <sup>b</sup>		MW (300 W) <sup>c</sup>	
		time (h)	yield (%) of <b>4</b> <sup>d</sup>	time (h)	yield (%) of <b>4</b> <sup>d</sup>
1	4-F-C <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	2	<b>4b</b> ; 60 (54)	0.5	<b>4b</b> ; 98 (92)
2	2-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	2	<b>4c</b> ; 56 (47)	2	<b>4c</b> ; > 99 (90)
3	3-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	1	<b>4d</b> ; 80 (66)	1	<b>4d</b> ; > 99 (85)
4	4-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	1	<b>4e</b> ; 75 (63)	1	<b>4e</b> ; > 99 (87)
5	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> ( <b>2f</b> )	2	<b>4f</b> ; 64 (52)	2	<b>4f</b> ; > 99 (87)
6	2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> ( <b>2g</b> )	2	<b>4g</b> ; 91 (78)	0.5	<b>4g</b> ; > 99 (86)
7	2-Cl-6-F-C <sub>6</sub> H <sub>3</sub> ( <b>2h</b> )	2	<b>4h</b> ; 79 (68)	0.75	<b>4h</b> ; 97 (86)
8	C <sub>6</sub> F <sub>5</sub> ( <b>2i</b> )	1	<b>4i</b> ; 98 (92)	0.5	<b>4i</b> ; > 99 (93)
9	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> ( <b>2j</b> )	2	<b>4j</b> ; 41 (34)	2	<b>4j</b> ; 86 (79)
10	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> ( <b>2k</b> )	2	<b>4k</b> ; 68 (60)	2	<b>4k</b> ; > 99 (91)
11	2-Me-C <sub>6</sub> H <sub>4</sub> ( <b>2l</b> )	2	<b>4l</b> ; 50 (40)	2	<b>4l</b> ; 96 (86)
12	3-Me-C <sub>6</sub> H <sub>4</sub> ( <b>2m</b> )	2	<b>4m</b> ; 72 (65)	1.5	<b>4m</b> ; 98 (91)
13	4-Me-C <sub>6</sub> H <sub>4</sub> ( <b>2n</b> )	1	<b>4n</b> ; 65 (56)	1	<b>4n</b> ; 97 (88)
14	4-OMe-C <sub>6</sub> H <sub>4</sub> ( <b>2o</b> )	2	<b>4o</b> ; 58 (47)	1.5	<b>4o</b> ; > 99 (88)
15	4-OCF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> ( <b>2p</b> )	2	<b>4p</b> ; 84 (73)	0.5	<b>4p</b> ; 97 (86)
16	4-SMe-C <sub>6</sub> H <sub>4</sub> ( <b>2q</b> )	1	<b>4q</b> ; 64 (55)	1	<b>4q</b> ; 92 (83)
17	2-naphthyl ( <b>2r</b> )	1	<b>4r</b> ; 70 (57)	1	<b>4r</b> ; 95 (82)
18 <sup>e</sup>	9-anthracenyl ( <b>2s</b> )	2	<b>4s</b> ; 34 (25)	1	<b>4s</b> ; 64 (55)
19	2-pyridil ( <b>2t</b> )	24	<b>4t</b> ; 8 (–)	1	<b>4t</b> ; > 99 (87)
20	3-pyridil ( <b>2u</b> )	1	<b>4u</b> ; 85 (74)	0.5	<b>4u</b> ; > 99 (88)
21	3-furyl ( <b>2v</b> )	2	<b>4v</b> ; 89 (80)	0.5	<b>4v</b> ; > 99 (90)
22	2-thienyl ( <b>2w</b> )	1	<b>4w</b> ; 95 (84)	0.5	<b>4w</b> ; 98 (87)

<sup>a</sup>All the reactions were performed under a N<sub>2</sub> atmosphere using 1 mmol of the corresponding aldoxime (0.33 M in a mixture water/glycerol (1:1)). Substrate/Ru ratio 100:5. <sup>b</sup>Reactions performed in a Teflon-capped sealed tube at 120 °C. <sup>c</sup>Reactions performed in a CEM Discover S-Class microwave synthesizer at 150 °C through moderation of the initial power (300 W). <sup>d</sup>Yields determined by GC. Isolated yields after appropriate chromatographic workup are given in parentheses. <sup>e</sup>Yields determined by <sup>1</sup>H NMR.

thienyl units, also participated in the reaction, delivering the corresponding primary amides **4r–4w** in good yields and short times using MW irradiation (64–99% GC yield after 0.5–1 h; 55–90% isolated yield after chromatographic purification; entries 17–22 in Table 3). Particularly striking is the case of the pyridine-2-carbaldoxime (**2t**), a substrate difficult to isomerize given its tendency to form strong metal chelates,<sup>49</sup> which was converted into picolinamide (**4t**) in almost quantitative yield after only 1 h of irradiation (entry 19). This result is in sharp contrast with that obtained when conventional thermal heating was used (only 8% GC yield after 24 h; entry 19), clearly highlighting the advantages of the MW irradiation. As in the case of **2a**, in all of the reactions collected in Table 3, complete consumption of the starting aldoximes was observed by GC, and the only byproducts detected were the corresponding organonitrile intermediates RC≡N (**3b–3w**).

To further confirm the generality of the process, the rearrangement of some aliphatic and  $\alpha,\beta$ -unsaturated aldoximes was subsequently explored (Table 4). Thus, as previously

**Table 4.** Rearrangement of Various Aliphatic and  $\alpha,\beta$ -Unsaturated Aldoximes Catalyzed by the Bis(allyl)-Ru(IV) Complex **1** in a Mixture of Water/Glycerol (1:1)<sup>a</sup>

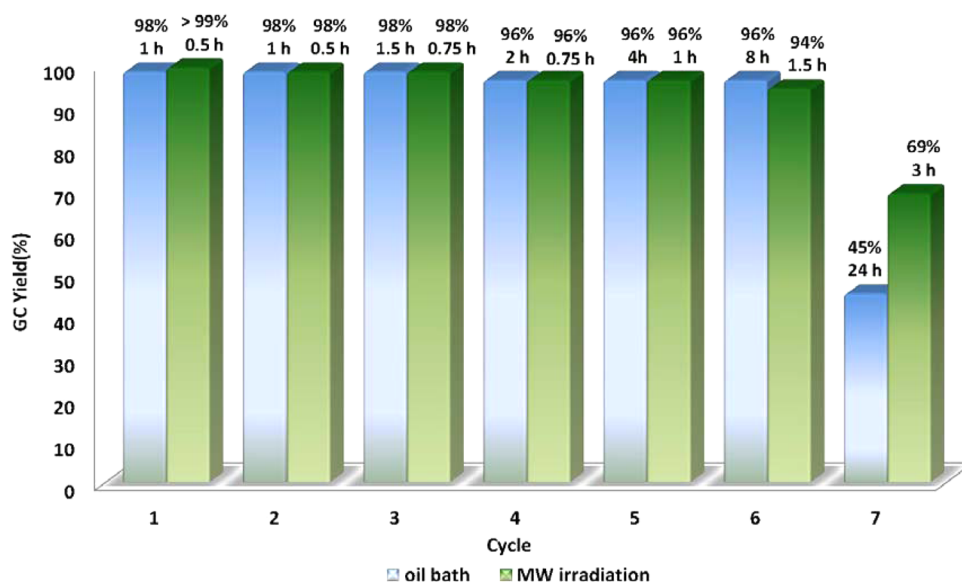
entry	aldoxime <b>2</b> (R)	oil bath <sup>b</sup>		MW (300 W) <sup>c</sup>	
		time (h)	yield (%) of <b>4</b> <sup>d</sup>	time (h)	yield (%) of <b>4</b> <sup>d</sup>
1	<i>n</i> -C <sub>5</sub> H <sub>11</sub> ( <b>2x</b> )	2	<b>4x</b> ; 75 (63)	1.5	<b>4x</b> ; 98 (86)
2	<i>n</i> -C <sub>6</sub> H <sub>13</sub> ( <b>2y</b> )	2	<b>4y</b> ; 74 (65)	2	<b>4y</b> ; 97 (88)
3	( <i>E</i> )-CH=CHPh ( <b>2z</b> )	1	<b>4z</b> ; 79 (68)	1	<b>4z</b> ; 68 (57) <sup>e</sup>
4	( <i>E</i> )-CH=CH-4-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>2aa</b> )	1	<b>4aa</b> ; 77 (68)	1.5	<b>4aa</b> ; 50 (41) <sup>e</sup>
5	( <i>E</i> )-CH=CH-2-OMe-C <sub>6</sub> H <sub>4</sub> ( <b>2ab</b> )	2	<b>4ab</b> ; 85 (78)	2	<b>4ab</b> ; 51 (44) <sup>e</sup>
6	( <i>E</i> )-CH=CH-4-OMe-C <sub>6</sub> H <sub>4</sub> ( <b>2ac</b> )	1	<b>4ac</b> ; 80 (72)	1	<b>4ac</b> ; 54 (46) <sup>e</sup>

<sup>a</sup>All the reactions were performed under a N<sub>2</sub> atmosphere using 1 mmol of the corresponding aldoxime (0.33 M in a mixture water/glycerol (1:1)). Substrate/Ru ratio 100:5. <sup>b</sup>Reactions performed in a Teflon-capped sealed tube at 120 °C. <sup>c</sup>Reactions performed in a CEM Discover S-Class microwave synthesizer at 150 °C through moderation of the initial power (300 W). <sup>d</sup>Yields determined by GC. Isolated yields after appropriate chromatographic workup are given in parentheses. <sup>e</sup>Varying amounts of the corresponding carboxylic acids were formed.

observed with the aromatic substrates, when hexanaldoxime (**2x**) and heptanaldoxime (**2y**) were subjected to the action of complex [ $\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-C}_{10}\text{H}_{16})\}_2$ ] (**1**), the application of MW irradiation led again to the generation of the corresponding amides **4x–4y** in higher yields (97–98% GC yield after 1.5–2 h; 86–88% isolated yield) to those achieved under classical oil-bath heating conditions (entries 1–2). As in the precedent cases, the formation of minor amounts of the respective nitriles **3x–3y** was also observed by GC, particularly when the latter reaction conditions were applied. However, in marked contrast with these results, when the  $\alpha,\beta$ -unsaturated aldoximes **2z–2ac** (entries 3–6) were employed as substrates, the use of MW irradiation at 150 °C significantly affected the selectivity of the process. In all these cases, the competitive formation of carboxylic acids as the result of the hydrolysis of the amides was observed. Therefore, the clear advantage that involves the use of MW irradiation in the rearrangement of aromatic and aliphatic aldoximes employing the bis(allyl)-Ru(IV) complex **1** as a catalyst was inextensible to  $\alpha,\beta$ -unsaturated aldoximes, in these cases the conventional thermal heating being much more effective (77–85% GC yield after 1–2 h; 68–78% isolated yield). Regardless of this, the high substrate scope and functional group tolerance of the process was fully demonstrated.

**Catalyst Recycling.** The insolubility of complex [ $\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-C}_{10}\text{H}_{16})\}_2$ ] (**1**) in the medium allows its separation





**Figure 2.** Rearrangement of pentafluorobenzaldoxime (**2i**) catalyzed by complex **1**: Catalyst recycling under thermal and MW irradiation conditions.

from the amide product by simple decantation. This fact prompted us to investigate the recycling of **1** using the rearrangement of pentafluorobenzaldoxime (**2i**) as a model reaction under thermal (5 mol % of Ru; 120 °C) and MW irradiation (5 mol % of Ru; 150 °C; 300 W) conditions. Thus, once the reaction finished, the liquid phase was decanted under heat. Subsequent cooling of this solution in an ice bath led to the crystallization of the pentafluorobenzamide (**4i**) product, which could be isolated in pure form by simple filtration. On the other hand, the precipitated solid catalyst was washed with a hot mixture of water and glycerol (1:1) and subsequently exposed to fresh substrate under the same experimental conditions. Almost quantitative conversions were reached during six consecutive cycles, using both thermal and MW irradiation conditions (see Figure 2), obtaining cumulative TON values of 125 and 130, respectively. However, an appreciable loss of catalytic activity was observed in each cycle. Indeed, 24 h of heating or 3 h of MW irradiation were needed in the seventh cycle to obtain the amide product in only 45 or 69% GC yield, respectively. This progressive decrease in the effectiveness of the process could be attributed to a partial forfeiture of the catalyst during the decantation procedure after each cycle. Again, the employment of MW irradiation represented an advantage over the classical oil-bath heating, since much lower reaction times were required to attain high conversions during the first six cycles.

In order to check the generality of this recycling procedure, the study was extended to other aromatic benzaldoximes using MW irradiation conditions (5 mol % of Ru; 150 °C; 300 W). Almost quantitative conversions were reached during six and four consecutive runs starting from 4-chlorobenzaldoxime (**2e**) and 2-thiophenecarbaldoxime (**2w**), respectively (cumulative TON values of 122 and 83; see Table 5). As in the precedent case, partial loss of activity was also observed after each catalytic cycle.

**Mechanistic Aspects.** From a mechanistic point of view, two different reaction pathways have been proposed for this catalytic transformation (see Scheme 3).<sup>44</sup> The first, and most commonly evoked, involves the initial coordination of the aldoxime **A** to the metal center through the nitrogen atom to form intermediate **B**, which evolves, via a dehydration process,

**Table 5.** Rearrangement of 4-Chlorobenzaldoxime (**2e**) and 2-Thiophenecarbaldoxime (**2w**) Catalyzed by Complex **1** under MW Irradiation Conditions: Catalyst Recycling<sup>a</sup>

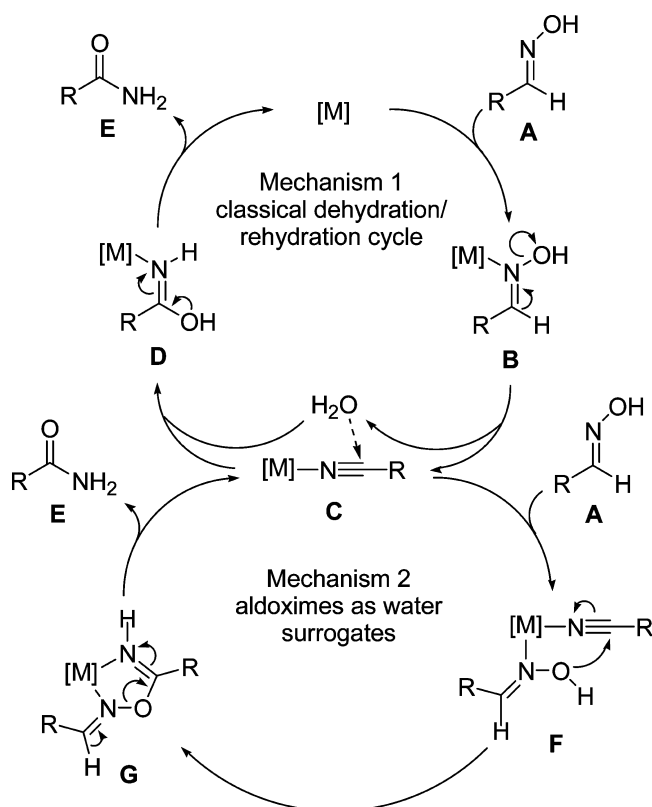
aldoxime <b>2</b> (R)	cycle	time (h)	yield (%) of <b>4</b> <sup>b</sup>	TON <sup>c</sup>
4-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	1	1	>99	20
	2	1	98	40
	3	1.25	96	59
	4	1.5	95	78
	5	1.5	93	97
	6	2	94	116
	7	5	30	122
2-thienyl ( <b>2w</b> )	1	0.5	98	20
	2	0.5	98	40
	3	0.5	96	59
	4	0.75	93	78
	5	5	27	83

<sup>a</sup>All the reactions were performed under a N<sub>2</sub> atmosphere using 1 mmol of the corresponding aldoxime (0.33 M in a mixture water/glycerol (1:1)) in a CEM Discover S-Class microwave synthesizer at 150 °C through moderation of the initial power (300 W). Substrate/Ru ratio 100:5. <sup>b</sup>Yields determined by GC. <sup>c</sup>Cumulative TON values.

into the corresponding nitrile complex **C**. Subsequent rehydration of **C** by the water released in the previous step (or from the solvent) leads to the iminol intermediate **D**. In the final step, an intramolecular hydrogen transfer induces the decoordination of the final amide **E** and regenerates the catalyst (see Mechanism 1 in Scheme 3). This proposal is usually sustained by the fact that the formation of free nitriles is generally observed during the course of the reactions, and by the well-known ability of transition metal complexes to promote the catalytic hydration of nitriles.

However, recent studies by Williams and co-workers employing <sup>18</sup>O isotopically labeled substrates have demonstrated, for a large number of metal catalysts, the operation of

Scheme 3. Proposed Mechanisms for the Catalytic Rearrangement of Aldoximes to Amides



an alternative mechanism involving a second molecule of aldoxime (instead of water) as the hydrating agent for intermediate **C** (Mechanism 2 in Scheme 3).<sup>54</sup> Thus, coordination of the aldoxime to **C** generates **F**, which evolves into the five-membered metallacycle **G** by intramolecular attack of the oxygen atom of the aldoxime on the carbon atom of the coordinated nitrile. Subsequent ring opening of this metallacycle leads to the final amide **E**, with regeneration of the nitrile complex **C**.

Taking into account these proposals, and in order to shed some light on the mechanism of action of our catalytic system, we decided to monitor our rearrangement reactions by GC. Thus, using the oil bath heating conditions (at 120 °C), which allows a better tracking of the catalytic process, a total consumption of the starting aldoximes in the early stages of the catalytic events was in all cases observed, 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 rearrangement of (*E*)-benzaloxime (**2a**) into benzamide (**4a**) is depicted in Figure 3.

As it can be seen in the graphic, (*E*)-benzaloxime (**2a**) is fully consumed after only 10 min of heating, with benzonitrile (**3a**; ca. 55% GC yield) and the final benzamide (**4a**; ca. 45% GC yield) being the only organic products present in solution. This fact clearly demonstrates that the hydration of the intermediate nitrile **3a** is the rate limiting step of the catalytic reaction. In this sense, the absence of (*E*)-benzaloxime (**2a**) after 10 min discarded a hydration mechanism assisted by a second molecule of aldoxime, and only a classical hydration pathway by the water molecules present in the medium can be evoked from that moment (Mechanism 1 in Scheme 3). However, a drastic decrease in the rate of the hydration process

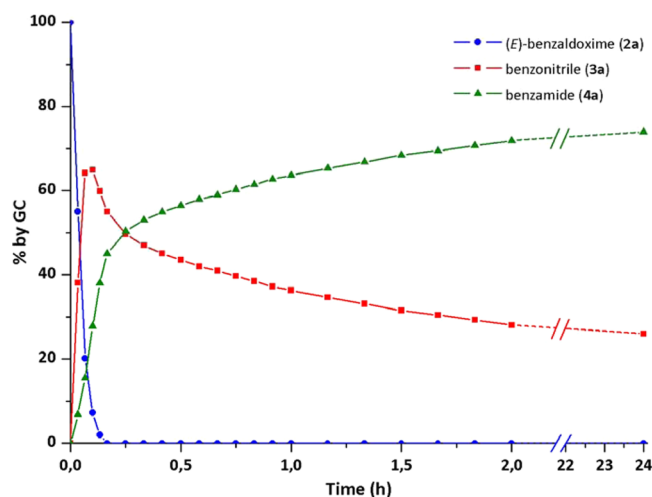


Figure 3. Product distribution as a function of time for the rearrangement of (*E*)-benzaloxime (**2a**) to benzamide (**4a**) catalyzed by complex  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**).

was observed after that time (a total of 24 h are needed to reach only a final 74% GC yield of **4a**). These two facts, namely the high initial reaction rate observed when the (*E*)-benzaloxime (**2a**) is still present in solution and the strong decay in the catalytic activity when the aldoxime completely disappears from the reaction media, seem to indicate that the Williams mechanism (Mechanism 2 in Scheme 3) is probably operative at the beginning of the reaction, while a classical dehydration/rehydration pathway acts in the last stage of the process.

## CONCLUSIONS

In this work, we have shown that the commercially available bis(allyl)-ruthenium(IV) dimer  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})\}_2]$  (**1**) is an efficient catalyst for the selective rearrangement of a large range of aldoximes to their corresponding primary amides in a mixture of water and glycerol (1:1), using conventional thermal heating or microwave irradiation as energy source, and without the assistance of any cocatalyst. As a general trend, the use of MW irradiation appeared as the most convenient methodology for the rearrangement of aromatic, heteroaromatic, and aliphatic aldoximes, while thermal heating seems to be more convenient for the  $\alpha,\beta$ -unsaturated ones. The reusability of complex **1** (up to six times) has also been demonstrated using various substrates. As commented in the Introduction of this manuscript, the “green” and atom-economical synthesis of amides is currently of prime interest for the chemical community. We believe that the work reported herein is a good contribution to the field, offering an efficient, simple, and sustainable protocol to perform the catalytic rearrangement of aldoximes to amides.

## EXPERIMENTAL SECTION

All reactions were performed under a nitrogen atmosphere using vacuum-line and standard Schlenk or sealed-tube techniques. All the reagents were purchased from commercial suppliers and used as received. GC measurements were performed on Hewlett-Packard HP6890 equipment using a Supelco Beta-Dex 120 column (30 m length; 250  $\mu\text{m}$  diameter). Chromatography workups were performed using Merck silica gel 60 (230–400 mesh).

**General Procedure for the Synthesis of Aldoximes.** Aldoximes **2b–2ac** (all of them known compounds) were synthesized by condensation of the corresponding aldehyde with  $\text{NH}_2\text{OH}\cdot\text{HCl}$  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 resulting residual oil was extracted with diethyl ether (ca. 200 mL). The crude product was purified by column chromatography over silica gel using diethyl ether/hexane (1:1) as an eluent. The identity of aldoximes **2b**–**2ac**, which were in general obtained in 70–80% yield as mixtures of the corresponding *E* and *Z* isomers, was confirmed by  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectroscopy.

**General Procedure for the Catalytic Rearrangement of Aldoximes under Conventional Thermal Conditions.** Under a nitrogen atmosphere, the corresponding aldoxime **2a**–**2ac** (1 mmol), water (1.5 mL), glycerol (1.5 mL), and the bis(allyl)-ruthenium(IV) catalyst  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})_2\}_2]$  (**1**; 0.0154 g, 0.025 mmol; 5 mol % of Ru) were introduced into a Teflon-capped sealed tube, and the reaction mixture was stirred at 120 °C in an oil bath for the indicated time. The course of the reaction was monitored regularly taking samples of ca. 20  $\mu\text{L}$ , which after extraction with  $\text{CH}_2\text{Cl}_2$  (3 mL) were analyzed by GC. Once the reaction finished, the insoluble catalyst was eliminated by filtration and the mixture of solvents eliminated under reduced pressure. The crude reaction mixture was subsequently purified by column chromatography over a silica gel using methanol/ $\text{CH}_2\text{Cl}_2$  mixtures as eluents. In some cases, direct crystallization from the water/glycerol mixture also allowed the isolation of pure products. The identity of the resulting primary amides was assessed by comparison of their NMR spectroscopic data with those reported in the literature.

**General Procedure for the Catalytic Rearrangement of Aldoximes under MW Irradiation Conditions.** Under a nitrogen atmosphere, the corresponding aldoxime **2a**–**2ac** (1 mmol), water (1.5 mL), glycerol (1.5 mL), and the bis(allyl)-ruthenium(IV) catalyst  $[\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})_2\}_2]$  (**1**; 0.0154 g, 0.025 mmol; 5 mol % of Ru) were introduced into a crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 150 °C (temperature monitored by a built-in infrared sensor), 300 W, and 100–120 psi (1 psi = 6.89 kPa) for the indicated time. The course of the reaction was monitored by regular sampling and analysis by GC. The purification of the final primary amides was performed following the same procedure described above.

**Catalyst Recycling.** After completion of the reaction, the liquid phase was decanted under heat and the insoluble solid catalyst washed with a hot mixture of water and glycerol (1:1; 3  $\times$  3 mL). Fresh aldoxime, water, and glycerol were then added following the reaction conditions described above.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.5b01107.

Copies of the NMR spectra of the primary amides synthesized in this work (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

Dedicated to Dr. Rajender S. Varma on the occasion of his 65th birthday

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