

## Rhodium Catalysis

 Rhodium-NHC-Catalyzed *gem*-Specific *O*-Selective  
 Hydropyridonation of Terminal Alkynes

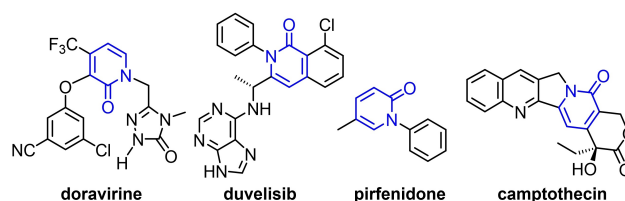
 María Galiana-Cameo, Raúl Romeo, Asier Urriolabeitia, Vincenzo Passarelli,  
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**Abstract:** The dinuclear complex  $[\text{Rh}(\mu\text{-Cl})(\eta^2\text{-coe})\text{-}(\text{IPr})_2]$  is an efficient catalyst for the *O*-selective Markovnikov-type addition of 2-pyridones to terminal alkynes. DFT calculations support a hydride-free pathway entailing intramolecular oxidative protonation of a  $\pi$ -alkyne by a  $\kappa^1N$ -hydroxypyridine ligand. Subsequent *O*-nucleophilic attack on a metallacyclopropene species affords an *O*-alkenyl-2-oxypyridine chelate rhodium intermediate as the catalyst resting state. The release of the alkenyl ether is calculated as the rate-determining step.

The 2-pyridone scaffold can be found in many biologically relevant compounds, including some drugs approved by the FDA for the treatment of cancer, HIV or pulmonary fibrosis (Scheme 1).<sup>[1]</sup> Classical multistep synthetic procedures<sup>[2]</sup> have been gradually substituted by more efficient metal-catalyzed approaches.<sup>[3]</sup> Thus, while reactivity on the *C*-sites mainly rely on *C*-H activation,<sup>[4]</sup> a diverse set of methods for heteroatomic functionalization have been described, including alkylation with organohalides,<sup>[5]</sup> the use of diazo compounds,<sup>[6]</sup> addition to unsaturated substrates,<sup>[7]</sup> or allylic substitution reactions.<sup>[8]</sup> However, the *N*- vs. *O*-selectivity is far to be controlled and critically depends on the reaction conditions or the ligands, partly as a result of 2-hydroxypyridine vs. 2-pyridone tautomerization.<sup>[9]</sup>

In particular, preparation of *O*- or *N*-alkenylated 2-pyridones presents unique challenges, especially for the *gem*-olefin derivatives (Scheme 2). Firstly, the access via the

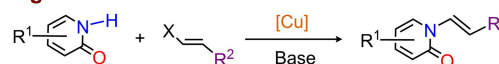
*O*-nucleophilic attack of enolates to 2-halogenated-pyridines is hampered. In addition, thermodynamically preferred *N*-substituted *trans*-isomers are prevalent when using alkenyl halides or boronic acids.<sup>[10]</sup> Other synthetic approaches, such as isomerization within an *O*-unsaturated chain,<sup>[11]</sup> *O*- to *N*-rearrangement,<sup>[12]</sup> or aldol condensation,<sup>[13]</sup> have limited generality lacking the formation of *gem*-isomers. The few existing preparative methods for *gem*-alkenyl pyridones involve multistep procedures<sup>[14]</sup> or the use of specific precursors such as tosylhydrazones<sup>[15]</sup> or benzyne,<sup>[16]</sup> therefore more reliable synthetic methods are desirable. In this context, the Markovnikov-addition of 2-pyridones to triple bonds seems a straightforward atom-economical access.



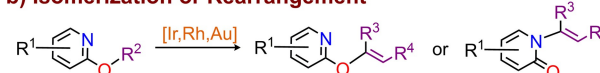
Scheme 1. Some 2-pyridone-based drugs approved by the FDA.

## General methods for alkenylation of 2-pyridones

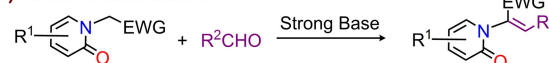
## a) Organohalides



## b) Isomerization or Rearrangement



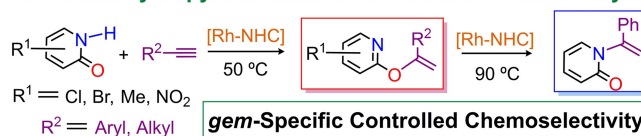
## c) Aldol Condensation



## d) Addition to Alkynes Bearing Powerful EWG or EDG



## Our Work: Hydropyridonation of Unactivated Terminal Alkynes



Scheme 2. Previous reports for preparation of *N*- or *O*-alkenylated 2-pyridones and our strategy.

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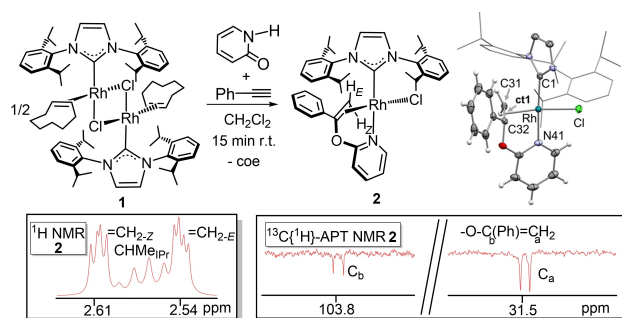
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However, direct addition proceeds only for alkynes bearing powerful EWG or EDG groups,<sup>[17]</sup> thus, we envisage a transition-metal catalyzed approach for unactivated terminal alkynes. Moreover, we anticipate the different affinity of rhodium for *O*- or *N*-donor functions as a potential tool to control chemoselectivity. Nevertheless, an important handicap for successful catalytic alkyne hydroxyridonation is the intrinsic high self-reactivity of terminal alkynes to give a myriad of dimeric, polymeric or cyclic structures.<sup>[18]</sup>

Our research group has recently disclosed efficient rhodium-*N*-heterocyclic carbene (NHC) catalysts for diverse carbon-heteroatom couplings via hydrofunctionalization of alkynes.<sup>[19]</sup> Particularly, the introduction of 2-pyridone in the Rh-NHC framework results in impressive TOFs for alkyne dimerization.<sup>[20]</sup> The 2-pyridonato ligand behaves as a fast proton shuttle between the two alkynes. Moreover, the specific *gem*-selectivity of 1,3-enynes arises from the preferred protonation at the terminal position of a  $\pi$ -coordinated alkyne. In the course of mechanistic studies involving  $[\text{Rh}(\mu\text{-Cl})(\eta^2\text{-coe})(\text{IPr})_2]$  (**1**) {IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazolin-2-carbene; coe = cyclooctene}, 2-pyridone, and phenylacetylene, we serendipitously observed the formation of a new Rh-IPr complex in small quantities. This compound has now been identified by X-ray diffraction analysis and multinuclear NMR spectroscopy as  $\text{RhCl}(\text{IPr})\text{-}[\kappa\text{N},\eta^2\text{-}\{\text{py-O-C}(\text{Ph})=\text{CH}_2\}]$  (**2**), featuring an unexpected *O*-alkenyl-2-oxypyridine chelate (Figure 1). Complex **2** was isolated in 79% yield by treatment of **1** with stoichiometric amounts of phenylacetylene and 2-pyridone. In the solid state, coordination of the alkenyl ether is shown by Rh–N41 [2.0891(15) Å] and Rh–ct1 distances [1.96913(15) Å] (ct1, olefin centroid). Moreover, the appearance of two doublets of doublets,  $\delta = 2.61$  ( $J_{\text{H-H}} = 4.3$ ,  $J_{\text{H-Rh}} = 2.8$  Hz) and 2.54 ppm ( $J_{\text{H-Rh}} = 2.1$  Hz), in the  $^1\text{H}$  NMR spectrum and two doublets, 103.8 ( $J_{\text{C-Rh}} = 18.6$  Hz) and 31.5 ppm ( $J_{\text{C-Rh}} = 15.5$  Hz), in the  $^{13}\text{C}\{^1\text{H}\}$ -APT NMR experiment, confirms the coordination of the geminal olefin in solution.

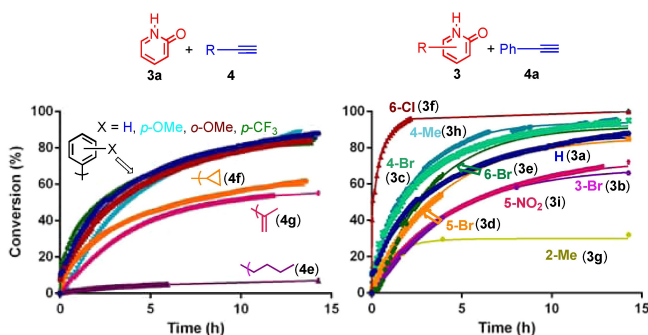
In view of the ability of **1** to promote the stoichiometric alkyne-pyridone C–O coupling, we next studied its application to catalytic alkyne hydroxyridonation. Gratifyingly, the



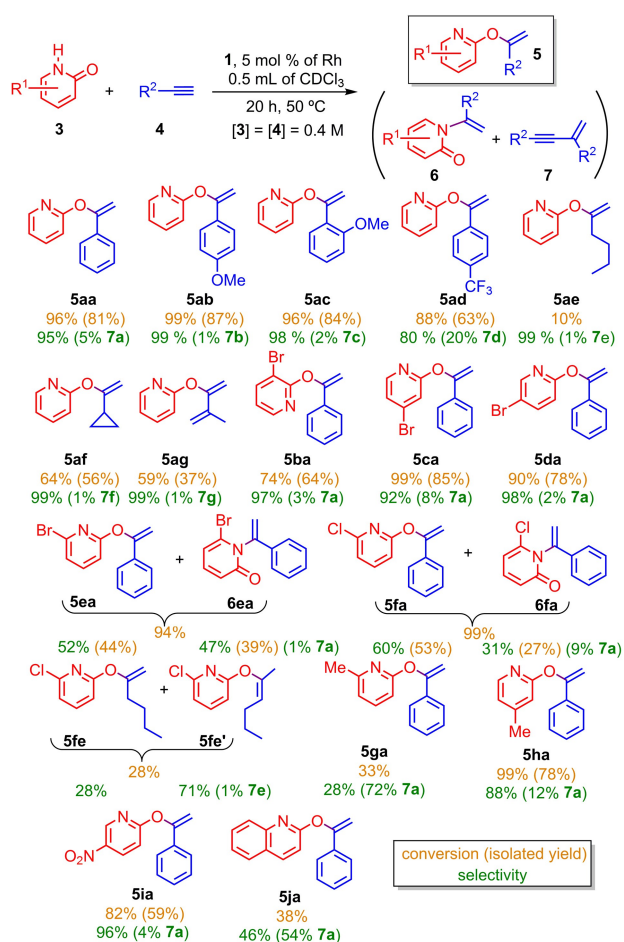
**Figure 1.** Formation of the chelate *O*-alkenyl-2-oxypyridine rhodium complex **2** and ORTEP view. For clarity a wireframe style is adopted for the NHC wingtips and most hydrogen atoms are omitted. Selected bond lengths [Å] are: Rh–C1 2.0193(18), Rh–Cl 2.3353(5), Rh–ct1 1.96913(15), C31–C32 1.408(3), Rh–N41 2.0891(15); ct1: centroid of C31 and C32.

addition of **1**, 5 mol % of Rh, to the benchmark substrates 2-pyridone (**3a**) and phenylacetylene (**4a**) in  $\text{CDCl}_3$  resulted in the formation of the *gem*-alkenyl ether 2-(1-phenylvinyl)oxypyridine (**5aa**), after 20 h at 40 °C, as the exclusive heterocoupling product. Only 8% of the 1,3-enyne arisen from competitive alkyne dimerization was observed. Other polar solvents were tested but alkyne dimerization prevailed (see Supporting Information). Temperature screening revealed a gradual reduction of alkyne conversion over 50 °C, likely due to catalyst decomposition, thus further experiments were performed at this compromise temperature. Interestingly, complex **2** was detected in the first monitoring spectrum. Indeed, similar catalytic outcome was obtained by using **2** as catalyst. Both facts suggest that **2** might be the resting state of the catalytic cycle. Moreover, the presence of an NHC was disclosed to be essential. The precursor of **1**,  $[\text{Rh}(\mu\text{-Cl})(\eta^2\text{-coe})_2]_2$ , was inactive, while the Wilkinson's catalyst  $\text{RhCl}(\text{PPh}_3)_3$  or the in situ formed  $[\text{Rh}(\mu\text{-Cl})(\text{BINAP})_2]$  favored alkyne dimerization vs. hydroxyridonation. It is worth a mention of the work of Breit's group showing the Rh-BINAP compound as efficient catalyst for the 2-pyridone addition to allenes.<sup>[7a]</sup> Other Rh-IPr complexes with  $\kappa^2$ acetato or CO ancillary ligands were inefficient.

As for the scope of alkyne hydroxyridonation promoted by **1**, catalytic reactions were monitored in NMR tubes using a 5 mol % of Rh and 1:1 pyridone:alkyne ratio in  $\text{CDCl}_3$  at 50 °C (Figure 2). Organic products were isolated after 20 h (Scheme 3). In general, *gem*-specific *O*-alkenylated derivatives **5** were obtained, with the exception of 6-halogenated-2-pyridone substrates (**3e,f**), which also gave *N*-alkenylated products **6** in variable amounts. Competitive alkyne dimerization was limited to 1–12% in cases of effective hydroxyridonation, except for 4-(trifluoromethyl)phenylacetylene (**4d**) (20%), which agrees with the faster alkyne dimerization previously observed for this alkyne.<sup>[20]</sup> Otherwise, inefficient substrates such as 6-methyl-2-pyridone or 2-quinolone produced higher amounts of 1,3-enyne. Regarding the functional groups, aromatic alkynes reacted faster than aliphatic ones, while no definite trend was observed for substituted 2-pyridones. The more divergent results were found for 6-substituted ones. Thus, 6-chloro-2-pyridone (**3f**) is the most



**Figure 2.** Reaction profile for the hydroxyridonation of alkynes with 2-pyridone (left) and phenylacetylene with functionalized 2-pyridone derivatives (right).



Scheme 3. Scope for the hydropyridonation of alkynes catalysed by 1.

active substrate in this study, whereas poor conversion was obtained for 6-methyl-2-pyridone (3g), with the bromo counterpart 3e lying in the middle. Substitution in other

positions had only moderate influence. The alkenyl ether arising from 6-chloro-2-pyridone and 1-hexyne was obtained as a mixture of two isomers as a result of terminal to internal olefin isomerization. Finally, 4-methyl-2-pyridone (3h) slightly overcame the catalytic activity of parent 2-pyridone, while 5-nitro-2-pyridone (3i) fell behind. Other bulky, heteroatomic-substituted propargyl derivatives or internal alkynes were catalytically inefficient.

Some control experiments were performed to identify the reaction mechanism. Addition of 2-pyridone and phenylacetylene to 1 at  $-60^\circ\text{C}$  resulted in the immediate formation of complex 2 and no other intermediates, including Rh–H species, could be detected. Besides, H/D exchange between the *N*-deuterated 2-pyridone and the terminal proton of phenylacetylene preclude us from obtaining accurate information from deuterium labelling experiments (See Supporting Information). Catalytic tests in which 2-pyridone was replaced by phenol, *N*-methyl-2-aminopyridine, 2-thiopyridine, or 2-(hydroxymethyl)pyridine were unproductive, indicating that the presence of both N and O atoms located at 1,3-positions is essential.

The mechanism of the alkyne hydropyridonation catalyzed by 1 was studied by DFT computational analysis using 2-pyridone and phenylacetylene as model substrates (Figure 3,  $\Delta G$  in  $\text{kcal mol}^{-1}$ ). A plausible first step is the  $\pi$ -alkyne and  $\kappa^1N$ -hydroxypyridine coordination to the labile precursor 1 to yield **A**, which has been selected as the energetic reference. The O–H oxidative addition seems unfeasible since the corresponding Rh–H species **K**, located  $13.7 \text{ kcal mol}^{-1}$  above **A**, requires to surmount a barrier of  $31.2 \text{ kcal mol}^{-1}$  (see Figure S124 in Supporting Information). Alternatively, we propose a hydride-free pathway entailing oxidative protonation and reductive coupling steps (Scheme 4).<sup>[20,21]</sup> Thus, the  $\kappa^1N$ -hydroxypyridine ligand of **A** can behave as an intramolecular Brønsted acid able to protonate the terminal position of the  $\pi$ -alkyne to form the Rh<sup>III</sup>-alkenyl species **B**, via **TSAB**. Protonation of internal position of the triple bond is disfavored

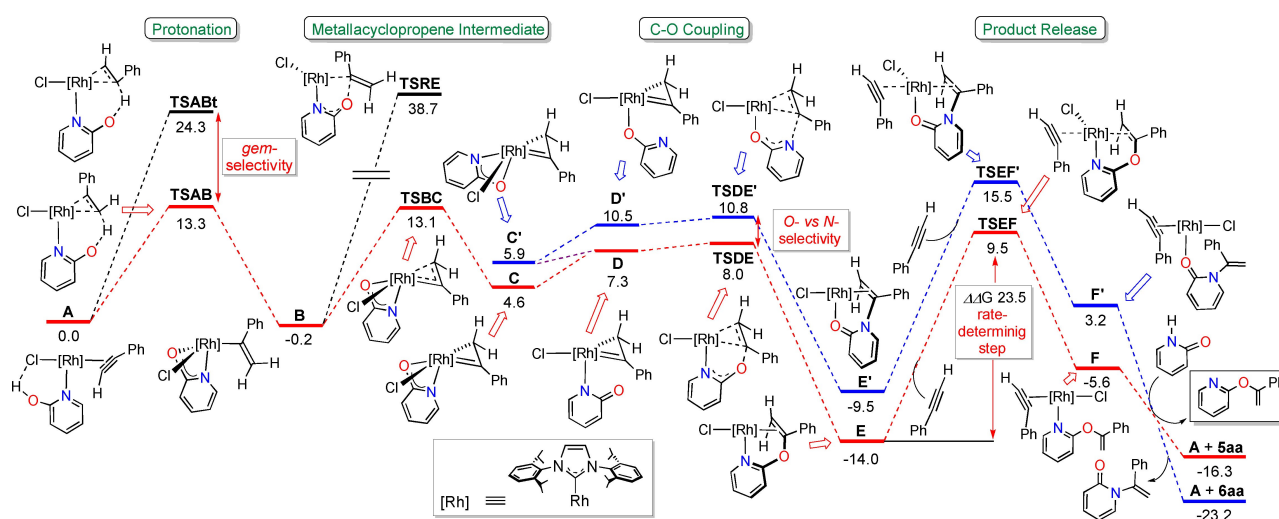
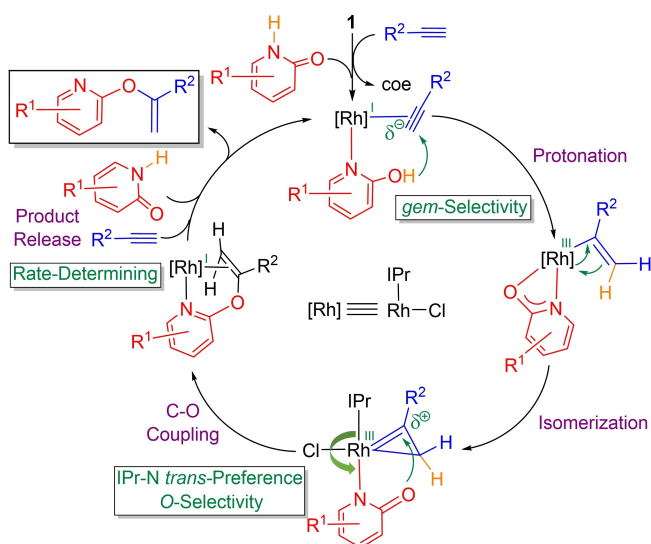


Figure 3. DFT energetic profile ( $\Delta G$  in  $\text{kcal mol}^{-1}$ , relative to **A** and isolated molecules) along hydropyridonation of phenylacetylene. O-alkenylation, red pathway, and N-alkenylation, blue pathway.





**Scheme 4.** Mechanistic proposal for alkyne hydroypyridonation.

(**TSABt**,  $\Delta\Delta G$  of  $11.0 \text{ kcal mol}^{-1}$ ), which ultimately determines the high *gem*-selectivity.

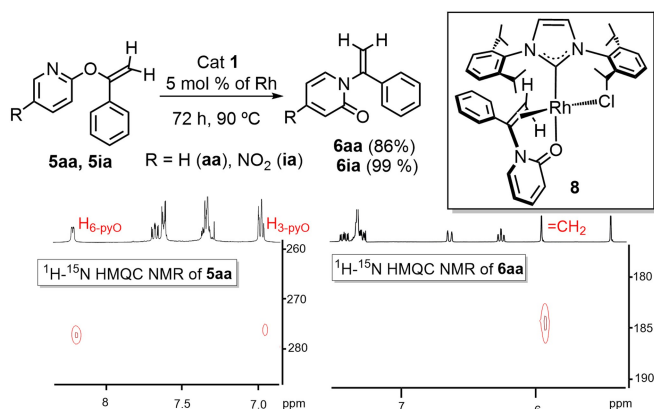
The direct C–O reductive coupling within **B** was found to be unaffordable under catalytic conditions,<sup>[22]</sup> which is in sharp contrast to that observed for alkenyl-alkynyl C–C coupling in alkyne dimerization.<sup>[20]</sup> However, the isomerization of the alkenyl derivative **B** to the metallacyclopropene species **C**, though destabilized by  $4.8 \text{ kcal mol}^{-1}$ , opens an accessible pathway to the *O*-alkenyl-oxypyridone species **E** ( $-14.0 \text{ kcal mol}^{-1}$ ), in agreement with the isolation of **2**. This stage entails the decoordination of the oxygen atom of the pyridonato (**C**→**D**) and subsequent *O*-nucleophilic attack, in turn facilitated by increased positive charge at the carbenic carbon atom of the metallacyclopropene in **D** (see Figure S131 in Supporting Information).<sup>[21c,23]</sup> In contrast, the attack of the nitrogen atom has a higher barrier (**TSDE'**,  $\Delta\Delta G$   $2.8 \text{ kcal mol}^{-1}$ ), in accordance with the preferential *O*-alkenylation. Most likely, the ultimate reason for the chemoselectivity could be the preferred coordination of a pyridine scaffold *trans* to IPr, thus causing a seesaw effect responsible of the *O*-nucleophilic attack.<sup>[24]</sup> Moreover, the particular stereoelectronic properties of the bulky powerful electron releasing IPr might play a role in the stabilization of metallacyclopropene species (See Figure S125 in Supporting Information for comparison with a  $\text{PPh}_3$  analogue). In fact, these uncommon structures can be considered as essential intermediates in the *gem*-selective alkyne hydroalkoxylation in analogy to the role played by vinylidenes in the formation of *E/Z* isomers.<sup>[25]</sup>

The catalytic cycle ends with the associative release of the alkenyl ether (**TSEF**,  $23.5 \text{ kcal mol}^{-1}$ ), which is the rate-determining step (see Figure S126 in Supporting Information). At this point, the interplay between steric hindrance and the high *trans* effect imparted by the NHC might trigger the release of the catalytic product from **2**.<sup>[19a]</sup> It is interesting to note that the final *N*-alkenyl product is more stable than the *O*-alkenyl one indicating a kinetic control under catalytic conditions. Calculations involving the 1-hexyne show a higher

barrier of  $25.9 \text{ kcal mol}^{-1}$ , consistent with the slower reaction rate. Besides, the higher rate observed for 6-chloro-2-pyridone **3f** is likely due to steric effects, which might be responsible for the decrease of the product release barrier, whereas the similar energies of **5fa** and **6fa** account for the formation of both isomers (See Supporting Information).

Analysis of the energetic profiles of Figure 3 reveals that isomerization of *O*-alkenyl-oxypyridones to thermodynamically preferred *N*-alkenyl derivatives is feasible by breaking back the C–O bond (overall barrier for **A**+**5aa**→**C** via **TSEF**:  $25.8 \text{ kcal mol}^{-1}$ ).<sup>[23a]</sup> Thus, heating isolated **5aa** or **5ia** in the presence of catalytic amounts of **1** for 72 h at  $90^\circ\text{C}$  resulted in the formation of the *N*-alkenyl-pyridone derivatives **6** (Figure 4). Formation of **6** was not observed when simply heating the NMR tube containing crude **5** from catalytic hydro-pyridonation, likely due to decomposition of active species. In fact, the isomerization did not proceed either in the absence of **1** or using  $[\text{Rh}(\mu\text{-Cl})(\eta^2\text{-coe})_2]_2$  as catalyst. Given the small difference in the chemical shift of intuitively representative  $\text{C}_2$ -imidic (**5aa**,  $\delta = 163.3 \text{ ppm}$ ) or  $\text{C}_2$ -amidic (**6aa**,  $\delta = 162.2 \text{ ppm}$ ) atoms in the  $^{15}\text{C}\{^1\text{H}\}$ -APT NMR spectra, the 2D  $^1\text{H}$ - $^{15}\text{N}$  long-range HMQC NMR experiment was key to the characterization of **6**. Thus, correlation between one olefinic proton and the nitrogen atom was observed for **6**, but it is absent in **5** where both atoms are located five bonds away. Similarly to the formation of **2**, the *N*-alkenyl-pyridone derivative **6aa** reacts with **1** to yield  $\text{RhCl}[\kappa\text{O},\eta^2\text{-}\{\text{C}_4\text{H}_4(\text{C}=\text{O})\text{N}\}\text{-C}(\text{Ph})=\text{CH}_2](\text{IPr})$  (**8**). Multinuclear NMR data agree with the proposed pyridone-alkenyl structure exhibiting a  $\kappa^1\text{O},\eta^2$ -coordination mode.

In conclusion, we have disclosed herein a Rh-NHC efficient catalytic system for *gem*-specific and *O*-selective alkyne hydroypyridonation. Mechanistic studies in combination with DFT calculations support a hydride-free pathway. After initial coordination of both substrates, intramolecular oxidative protonation at the terminal position of a  $\pi$ -alkyne by a  $\kappa^1\text{N}$ -hydroxypyridine ligand is responsible for *gem*-specificity. Since direct C–O reductive elimination within the resulting alkenyl-pyridonato intermediate was found to be unaffordable, isomerization to a metallacyclopropene species opens the way to nucleophilic attack. Chemoselectivity control towards the less



**Figure 4.** *O*- to *N*-alkenyl isomerization and  $^1\text{H}$ - $^{15}\text{N}$  HMQC NMR correlations.

thermodynamically favoured *O*-alkenylated products arises from the preferred *N*- vs. *O*-coordination of the  $\kappa^1$ pyridonato ligand in Rh-IPr systems. In addition, the key role of the bulky electron-releasing IPr ligand in the stabilization of the metal-lacyclopropene species has been identified. Research efforts are underway for the design of more efficient catalysts that will open future opportunities for functionalization of other biologically active heterocycles.

### Acknowledgements

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### Conflict of Interest

The authors declare no conflict of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** Alkenylation · Alkyne Hydrofunctionalization · C–O Coupling · N-Heterocyclic Carbene · Pyridone

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