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Rhodium(III)-Catalyzed C–H Activation/Heterocyclization as a Macrocyclization Strategy. Synthesis of Macrocyclic Pyridones

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Supporting Information Placeholder

ABSTRACT: Structurally diverse macrocyclic pyridones can be efficiently synthesized by a rhodium(III)-catalyzed C–H activation/heterocyclization of ω -alkynyl α -substituted acrylic hydroxamates. The use of a *O*-pivaloyl hydroxamate as directing group was crucial to achieve efficient catalyst turnover in a redox-neutral process.

Transition metal-catalyzed reactions proceeding with C–H activation constitute a class of transformations that have tremendously impacted the field of organic synthesis and provided new opportunities for constructing heterocycles in an atom- and step-economic manner.¹ In recent years, macrocycles have aroused considerable interest in medicinal chemistry because these compounds can be potentially used as probes or drugs to target protein-protein interactions.² Within the quest for innovative strategies toward structurally diverse macrocycles, activation of C–H bonds can be of interest, compared to conventional macrocyclizations of α,ω -difunctionalized acyclic precursors, although examples are still scarce.³ Macrolactones **A** have been prepared by intramolecular palladium-catalyzed C–H allylic oxidation,⁴ or rhodium-catalyzed redox-neutral C–H propargylic oxidation,⁵ whereas intramolecular palladium-catalyzed C–H arylations or heteroarylations have been used to construct macrocycles **B**.^{6,7} Recently, aza-macrocycles **C** have been synthesized by an intramolecular rhodium-catalyzed amination (Scheme 1).^{8,9} We previously reported an intramolecular version of the ruthenium(II)-catalyzed heterocyclization of benzhydroxamates with alkynes,^{10,11} applied to substrates **D**, that allowed an efficient access to macrocyclic isoquinolones **E** (Scheme 1, eq 1).¹² Compared to the intermolecular redox-neutral process which normally operates in the case of benzhydroxamates (N–O cleavage),^{10,11} the presence of an external oxidant such as Cu(OAc)₂,¹³ in conjunction with the portionwise addition of ω -alkynyl benzhydroxamates **D**, were crucial to ensure catalyst turnover.¹² To expand the scope of macrocyclizations proceeding with C–H activation and formation of a heterocyclic scaffold,

pyridones emerged as appealing targets because of their wide occurrence in bioactive compounds.¹⁴

Herein, we report our investigations on the development of the rhodium(III)-catalyzed macrocyclization of ω -alkynyl α -substituted acrylic hydroxamates **F** into macrocyclic pyridones **H**,¹⁵ occurring through metallacycle intermediates **G** and a redox-neutral process (Scheme 1, eq 2).

Scheme 1. Macrocyclization by C–H Activation

Acrylic hydroxamates **F**, which should allow for milder reaction conditions than acrylamides,¹⁵ were selected as substrates and our studies began by investigating the reactivity of ω -alkynyl *O*-methyl hydroxamate **1**. Under the conditions of the ruthenium(II)-catalyzed macrocyclization, previously tuned-up for benzhydroxamates **D** {[RuCl₂(*p*-cymene)]₂ (10 mol %), MesCO₂K (60 mol %), Cu(OAc)₂·H₂O (2 equiv), CHCl₃ (final concentration, *c* 0.02 M), reflux},¹² conversion of substrate **1** into the desired macrocyclic pyridone **2** was extremely sluggish. The best result was obtained by achieving a slow addition of **1** (portionwise over 5 h) but macrocyclic pyridone **2** was isolated in 35% yield only, despite complete conversion of the substrate.¹² The use of a rhodium(III) catalyst¹¹ was immediately considered and we observed that the slow addition of **1** (*via* syringe pump over 0.5 h) to a solution of [Cp*RhCl₂]₂ (5 mol %) and CsOAc (30 mol %) in MeOH (reflux, 0.75 h) led to complete conversion and afforded the 12-membered pyridone **2** in 67% isolated yield (Scheme 2).

Scheme 2. Ru(II)- and Rh(III)-Catalyzed Macrocyclization of *O*-methyl hydroxamate **1**

^a Added portionwise or *via* syringe-pump.

This latter result clearly highlighted the superiority of the rhodium(III) over the ruthenium(II) catalytic system. However, the presence of a catechol linker in substrate **1** may facilitate the macrocyclization and thus the reaction conditions had to be evaluated with other substrates. Under the rhodium(III)-catalyzed conditions, disappointing results were indeed obtained with ω -alkynyl acrylic *O*-methyl hydroxamate **3**, devoid of a catechol linker, which was not efficiently converted (< 10%) into the 14-membered pyridone **4** (5%). The catalytic activity appeared to decay rapidly, as observed in the ruthenium-catalyzed macrocyclizations in the absence of additive.¹² The reaction was therefore conducted in the presence of Cu(OAc)₂·H₂O (50 mol %)^{11g,13} and this latter additive restored the catalytic activity as a complete conversion of substrate **3** occurred. However, the isolated yield of pyridone **4** was modest (28%) because the major product was the *N*-methoxy analog **5** (55%), which has to be inconveniently separated by flash chromatography. Thus, during the intramolecular heterocyclization of ω -alkynyl hydroxamate **3**, Cu(OAc)₂ not only helps to regenerate the Rh(III) catalyst by assisting the reductive elimination/N–O bond cleavage (redox-neutral process)¹³ leading to pyridone **4**, but also oxidizes Rh(I) species by an outer-sphere mechanism after the release of *N*-methoxy pyridone **5** in the reaction medium. Fagnou *et al.* previously showed that a *O*-pivaloyl hydroxamate could behave as a more reactive directing group and internal oxidant than the

O-methyl analog, thereby allowing for milder reaction conditions and a wider substrate scope.^{11f} This modification of the hydroxamate substituents has a spectacular effect on the efficiency of the rhodium(III)-catalyzed macrocyclization, as illustrated in the case of *O*-pivaloyl substrate **6** which afforded pyridone **4** in 74% yield, in the absence of additive.¹⁶ The macrocyclization of hydroxamate **7**, possessing a terminal alkyne,^{11f} was also remarkably efficient as the 14-membered disubstituted pyridone **8** was isolated in 94% yield in a reaction conducted at the gram-scale (Scheme 3).

Scheme 3. Comparison of the Reactivity of *O*-methyl and *O*-pivaloyl hydroxamates

It is worth mentioning that a minor regioisomeric pyridone **4'** (**4**/**4'** = 80:20) was detected by NMR analysis of the crude material arising from the macrocyclization of *O*-pivaloyl hydroxamate **6**, and this latter by-product was isolated in 15% yield (Scheme 4).¹⁷ In the commonly accepted (simplified) mechanism,¹⁰ rhodacycle [Rh]-**1** arising from a concerted metalation-deprotonation of **6** directed by the hydroxamate, would undergo migratory insertion of the alkyne to generate complex [Rh]-**2**. Reductive elimination and insertion of the metal into the N–O bond would produce complex [Rh]-**3** and release the Rh(III) catalyst and pyridone **4**. A Rh(V) nitrene, [Rh]-**4**, may also be involved as an intermediate.¹⁸ If migratory

Scheme 4. Formation of Regioisomeric Pyridones **4** and **4'**

insertion of the alkyne is retarded, as it may be the case in macrocyclizations, rhodacycle [Rh]-**1** may evolve into the Rh(V) nitrene [Rh]-**5**¹⁸ which would undergo rearrangement into Rh(III) isocyanate complex [Rh]-**6**. Subsequent migratory insertion of the alkyne and of the isocyanate would ultimately produce complex [Rh]-**7**, thereby accounting for the observation of pyridone **4'** (Scheme 4). Although the formation of regioisomeric pyridones such as **4'**, arising from an apparent hydroxamate-isocyanate rearrangement followed by heterocyclization,¹⁹ was generally a minor side process in most of the other examples of rhodium-catalyzed macrocyclizations investigated, this observation was noteworthy.

The macrocyclization of ω -alkynyl acrylic hydroxamates **9a–9j**, devoid of a catechol linker and possessing different aryl and heteroaryl substituents on the alkyne, was then studied. In all cases, complete conversions were observed. Pyridone **10a**, arising from the phenyl-substituted alkyne **9a**, was isolated in excellent yield (86%). For substrates **9b–9e**, we noticed that the more electron-withdrawing the substituent at the *para* position of the aromatic ring, the lower the yield of the corresponding pyridones **10b–10e**. This trend was apparent from the formation of **10b** (72%) and **10c** (64%), substituted respectively by a bromine atom or a CF₃ group, both having a negative inductive effect, and pyridones **10d** (59%) and **10e** (44%) bearing strongly attractive mesomeric acetyl and nitro groups. Conversely, pyridones **10f** (77%)²⁰ or **10g** (78%), possessing a mesomeric donor methoxy substituent at the *para* or the *ortho* position of the aromatic ring, were obtained in higher yields. These latter results were in agreement with previous observations that electron-rich diaryl alkynes are preferred partners in the Rh(III)-catalyzed hetero-cyclization of benzamides whilst the opposite trend is observed in the Ru(II)-catalyzed process.^{10,11} The behavior of heteroaryl-substituted alkynes **9h–9j** was next explored. Although pyridones **10h** (21%) and **10i** (41%) possessing 2-thienyl and 6-chloropyridin-2-yl substituents, respectively, were isolated in modest yields, substrate **9j** armed with the electron-rich *N*-Boc indolyl group led to macrocyclic pyridone **10j** in 81% yield (Scheme 5).

Scheme 5. Synthesis of 12-membered Pyridones 10a–10j

A nitrogen atom can be incorporated within the chain, as illustrated by the macrocyclization of carbamate **11** leading to the 12-membered aza-macrocyclic pyridone **12** (81%) (Scheme 6, eq 1). Macrocycles of larger ring-sizes and pos-

sessing an additional heterocyclic scaffold seem also accessible by this strategy, as exemplified by the macrocyclization of **13** incorporating a triazole, which afforded the 21-membered pyridone **14** (32%) (Scheme 6, eq 2). Although the yield is modest, this latter result illustrates that the combination of a copper-catalyzed azide-alkyne cycloaddition for the preparation of acyclic ω -alkynyl acrylic hydroxamates and the rhodium-catalyzed cyclization may constitute an interesting approach toward diversely substituted macrocyclic pyridones.

Scheme 6. Synthesis of Macrocyclic Pyridones 12 and 14

Pyridones can also be used as precursors of substituted pyridines, which are arguably the most encountered heterocycles in drugs.²¹ To that effect, pyridone **4** was converted into heteroaryl triflate **15** (94%)²⁰ which was subsequently involved in an aromatic nucleophilic substitution with aminoacetaldehyde dimethyl acetal to produce the 14-membered tetrasubstituted aminopyridine **16** (68%). Triflate **15** was also engaged in a Suzuki-Miyaura coupling with 2-methoxyphenylboronic acid and the 14-membered *meta*-pyridinophane **17** was isolated in 74% yield (Scheme 7).

Scheme 7. Synthesis of Macrocyclic Pyridines 16 and 17

In conclusion, we have demonstrated that the rhodium(III)-catalyzed macrocyclization of ω -acetylenic α -substituted acrylic hydroxamates, proceeding with C–H activation and intramolecular heterocyclization, can lead to structurally diverse 12- to 21-membered macrocyclic pyridones in moderate to excellent yields. The use of a *O*-pivaloyl hydroxamate as directing group was crucial to ensure efficient catalyst turnover in a redox-neutral process. These results contribute to further expand the scope of macrocyclizations proceeding with C–H activation and enabling formation of heterocyclic scaffolds of utmost importance in agrochemistry or medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization for all products, copies of the NMR spectra (PDF) and cif files.

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- (17) The structure of **4** and **4'** was assigned by X-ray diffraction analysis of the corresponding regioisomeric triflates **15** and **15'**, see Supporting Information.
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- (20) CCDC 1542219 (**10f**), 1542220 (**15**) and 1542221 (**15'**) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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