Catalytic Cyclization of o-(Alkynyl)Phenethylamines via Osmacyclopropene Intermediates: A Direct Access to Dopaminergic 3-Benzazepines


Dedication This article is dedicated to Prof. Antonio Echavarren on occasion of his 60th birthday

Abstract: A novel osmium-catalyzed cyclization of o-(alkynyl)phenethylamines to 3-benzazepines is reported. The procedure allows for the easy preparation of a broad range of dopaminergic 3-benzazepine derivatives. The investigation of the mechanism has revealed that the process takes place through osmacyclopropene intermediates, which have been isolated and X-ray characterized.

The design of efficient procedures for the preparation of seven-membered 3-benzazepines is challenging, since they remain as one of the most reliable structural scaffolds in terms of affinity and selectivity against the D1 receptor, which is the most important and abundant in the mammalian brains for the dopamine neurotransmitter.[1] In this context, transition metal-mediated C-N bond formation strategies offer advantages in comparison with the classical synthesis of heterocycles, such as mild reaction conditions, readily accessible starting materials, and user friendly procedures.[2] For instance, the intramolecular hydroamination and hydroamidation of alkynes has been a successful atom economic approach for the formation of N-heterocycles.[3] Unfortunately, only a few efficient syntheses of seven-membered rings are known. This is mainly due to the scarce number of specific transition metal catalysts developed for these reactions and the little understanding of the mechanism of the processes, as a consequence of the very low number of intermediates that have been isolated and characterized.[4]

Typically, two general mechanisms have been considered:[5] (I) amine route, and (II) alkyne route (Scheme 1). The first of them is initiated by N-H activation and includes the participation of Zr-amido route, and (II) alkyne route (Scheme 1). The first of them imido species, which afford cyclic imines by [2+2] cycloaddition

between the C-C triple bond of the alkyne moiety and the imido N-M double bond (path a, Scheme 1).[6] or the formation of Ru-, Sm-, Y- and Zn-amido intermediates, which evolve by insertion of the C-C triple bond into the N-M single bond (path b, Scheme 1).[7] The alkyne route implies the initial α-coordination of the C-C triple bond to the metal center, and it has been proposed for the Au-catalyzed 7-exo-dig cyclization of terminal alkylnitrosylamides (path c, Scheme 1).[8] The formation of diazepones and oxazepines by means of Pt- and Au-mediated 7-endo-dig cyclization of alkylnitrosylamides and diamidines,[9] and the Au- and Pd-catalyzed 7-endo-dig cyclization of o-(alkynyl)phenylacetamides to the corresponding benzazepinones (path d, Scheme 1).[10] We now report a new Os-catalyzed 7-endo-dig cyclization of terminal o-(alkynyl)phenethylamines (1) to 2,3-dihydro-1H-benz[d]azepines (2; commonly 3-benzazepines) that proceeds via a novel mechanism (III in Scheme 1) involving two metallocyclopropene intermediates, both of which have been isolated and characterized by X-ray diffraction analysis.

Scheme 1. Metal-catalyzed intramolecular hydroaminations and hydroamidations towards seven-membered nitrogenated heterocycles.

In the search for a specific catalyst and the optimum experimental conditions to perform this challenging cyclization, ruthenium, rhodium and platinum catalysts were initially employed, using N-(2-ethylphenethyl)propane-1-amine (1a) as model substrate (Table 1). We began with complex CpRuCl(PPh3)2, which has been found be the optimal catalyst for the 5- and 6-endo cyclization of aromatic homo- and bis-homopropargylic amines and amides to indoles,
dihydrodiquinoines and dihydroquinolines. Encouragingly, the regioselective 7-endo cyclization of 1a in pyridine occurred to give the desired 3-benzazepine 2a, albeit in a low yield (run 1). Similar result was found with the bulkier and electron richer catalyst Cp*RuCl(PPh3)2 (run 2). The presence of pyridine is mandatory since its removal is detrimental for the reaction (run 3), even though a stoichiometric amount is enough (run 4). The reaction yield decreased when the bulkier 2-picoline was used (run 5), showing the importance of the pyridine as both a base and a ligand. Modification of the electronic nature of the catalyst by using the ruthenium salt [CpRu(py)3]PF6 or a combination [CpRu(CH3CN)3]PF6/ bypyridine, recently used for the anti-Markovnikov hydration of alkynes, were detrimental for the reaction (runs 6 and 7). Finally, reactions performed with [RhCl(COD)]2/(4-FC6H4)3P (run 8) and PtCl2 (run 9) were unsuccessful.

Table 1. Optimization of the reaction

<table>
<thead>
<tr>
<th>Run</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CpRuCl(PPH3)2</td>
<td>Py</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>Cp*RuCl(PPH3)2</td>
<td>Py</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>CpRuCl(PPh3)2</td>
<td>Toluene/</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>CpRuCl(PPh3)2</td>
<td>Toluene/Py (1 equiv)</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>CpRuCl(PPH3)2</td>
<td>Toluene/Py (1 equiv)</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>[CpRu(py)3]PF6</td>
<td>Py</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>[CpRu(CH3CN)3]PF6/ Ligan[^d]</td>
<td>DMF</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>[Rh(cod)Cl]/(4-FC6H4)3P</td>
<td>Py</td>
<td>_[^n]</td>
</tr>
<tr>
<td>9</td>
<td>PtCl2</td>
<td>DCE</td>
<td>_[^n]</td>
</tr>
<tr>
<td>10</td>
<td>[CpOs(py)3]PF6 (3)</td>
<td>Py</td>
<td>57(51)[^f]</td>
</tr>
<tr>
<td>11</td>
<td>[CpOs(CH3CN)2(PPh3)]PF6</td>
<td>Py</td>
<td>52</td>
</tr>
</tbody>
</table>

[^a] Typical reaction conditions: catalyst (10 mol %), 90 °C, 24 h, [^a] = 0.05 M. [^b] Yields calculated by 1H NMR using trimethoxybenzene as internal standard. [^c] Ligan 5,5'-bis(4-fluoromethyl)-2,2'-bipyridine. [^d] Starting material recovered. [^e] Complex mixture. [^f] In parenthesis, isolated yield. Pic = 2-picoline.

Osmium has received little attention in catalysis, although its stoichiometric chemistry is very rich. Traditionally, it has been used to stabilize models of reactive intermediates proposed in reactions catalyzed by ruthenium and other metals. However, recent findings have demonstrated that it is a promising alternative to the classical metal catalysts, in particular for promoting some environmental friendly reactions. Five years ago, we showed that complex [CpOs(py)3]PF6 (3) is a more efficient catalyst than tungsten, ruthenium, and rhodium for the regioselective 7-endo heterocyclization of aromatic alkynols into benzazepines. Beller and co-workers have recently reported a high regioselective and general osmium-mediated hydroformylation of olefins to aldehydes. These precedents prompted us to employ osmium complexes as catalysts, in view of the little efficiency of the tested ruthenium complexes. Gratifyingly, when the cyclization of 1a was performed in the presence of a catalytic amount of complex 3, the 3-benzazepine 2a was formed in a fairly good yield (run 10). Similar results were achieved by using the electron richer catalyst [CpOs(CH3CN)2(PPh3)]PF6 (4); run 11). Hence the reaction conditions shown in run 10 were chosen for subsequent examination of the substrate scope of this transformation.

![Figure 1. Os-catalyzed heterocyclization of o-(alkynyl)phenethylamines 1b-p towards 3-benzazepines 2b-p](image)

We firstly examined the electronic effect of substituents, typically involved in dopaminergic properties, on the efficiency of the method. As illustrated in Chart 1, the heterocyclizations generally proceed in fairly good yields with monosubstituted electron rich and electron poor (para- or meta-substituents to the alkynyl) to give 3-benzazepines 2b-e. To our delight, disubstituted alkoxy derivatives 1f-h smoothly and cleanly undergo the 7-endo heterocyclization to the corresponding 3-benzazepines 2f-h in good-to-excellent yields as compared to the monoalkoxy derivatives due, most likely, to the higher stability under the reaction conditions. By contrast, the less electron rich dimethyl phenethylamine 1i gave a moderate yield of dialkylated 3-benzazepine 2i.

We subsequently evaluated the influence of different substituents on the amine, in order to favor future manipulations on the 3-benzazepines. Thus, while N-benzyl derivatives of parent or dimethoxy phenethylamines 1j and 1k gave moderate yields of the corresponding 3-benzazepines 2j,k, the electron-richer N-(3,4-dimethoxy) benzyl or phenethyl derivatives of parent phenethylamine 1l and 1m cyclized smoothly to the corresponding 3-benzazepines 2l and 2m in fairly good yields. Phenethylamines bearing bulkier secondary N-alkyl substituents 1n-p, also cyclized to the corresponding 3-benzazepines 2n-p, although in low to moderate yields.

Pyridine plays a main role in the catalysis. In order to isolate some reaction intermediates which allow us to obtain information about the reaction mechanism, we decided to study the
The X-ray structure of 5\(^{[19]}\) proves the formation of the osmacyclopropene moiety, which implies the oxidation of the metal center by two units. Thus, the distribution of ligands around the metal center is the expected one for a cyclopentadienyl-osmium (IV) species and can be described as a four-legged piano-stool geometry, with the cyclopentadienyl group occupying the three membered face whereas the C(1) and C(2) atoms of the metalacycle, the hydride ligand, and the phosphine lie in the four-membered face. The Os-(C1) and Os-(C2) bond lengths of 1.941(6) and 2.219(8) Å, respectively, compare well with those found in other osmacyclopropene compounds\(^{[20]}\) and support the double and single character of the bonds. In agreement with this, the \(^{13}\)C(\(^{1}\)H) NMR spectrum contains a low field C(1)-resonance at 207.5 ppm and a high field C(2)-resonance at -12.7 ppm. In the \(^1\)H NMR spectrum the most noticeable signal is the corresponding to the hydride ligand, which is observed at -13.73 ppm as a doublet with a H-P coupling constant of 33 Hz.

Complex 5 is certainly a species of the catalytic cycle. As a proof of concept, it catalyzed the heterocyclization of 1a to give 2a in 62% yield, after 24 h, under the same experimental conditions as those employed for the reaction with 4 (Table 1, run 11). The formation of this intermediate can be rationalized according to Scheme 3, which summarizes a mechanistic proposal for the catalysis, on the basis of the stoichiometric cycle shown in Scheme 2. The addition of the substrate to the metal center should produce the tautomerization of the carbon-carbon triple bond to initially afford the vinylidene I. Thus, according to the respective electrophilic and nucleophilic nature of the C\(_{\alpha}\) and C\(_{\beta}\) atoms, the carbon-carbon double bond of the allene could add the N-H bond of the amine function\(^{[21]}\) to give the azacycloalkylidene II, which should evolve into 5 by oxidative addition of one of the C-H bonds of the seven-membered ring.

The M-alkylidene to M-olefin rearrangement is present in many catalytic transformations, and it is particularly favored when the alkylidene has a C-H bond as here.\(^{[22]}\) Complex 5 is the key intermediate in the M-alkylidene to M-olefin transformation involved in this case (II $\rightarrow$ 5 $\rightarrow$ 6 $\rightarrow$ III $\rightarrow$ IV), which is promoted by pyridine. The hydride ligand in 5 if fairly acidic, as a consequence of the cationic nature of the complex. Thus, it should undergo deprotonation by action of the basic solvent, to afford 6. This compound would be in equilibrium with the \(\eta^2\)-cycloalkenyl intermediate III. In this context, it should be noted that the metalacyclopropene to metal-alkenyl transformation implies a simple C-C\(_{\beta}\) dissociation. Once intermediate III has been formed, protonation of the C\(_{\beta}\) atom of the alkenyl ligand by the pyridinium, generated previously by deprotonation of 5, could afford olefin derivative IV, regenerating the catalyst and releasing the reaction product.

Intermediate 6 was also isolated and characterized by X-ray diffraction analysis.\(^{[19]}\) As expected, the addition of 1.0 equiv of KÔBu to tetrahydrofurane solutions of 5, at room temperature, produces the deprotonation of the metal center and the formation of 6, which was isolated as an orange solid in 88% yield. Figure 1b shows a view of its structure. The most interesting feature is the disposition of the C(2)-H bond which, in contrast to 5, points away from the cyclopentadienyl ligand. The inversion of the configuration of C(2) is a strong indirect evidence in favor of the \(\eta^1\)-alkenyl intermediate III, since the process requires the rupture of the Os-C(2) bond of 6. Furthermore, in agreement with the cycle shown in Scheme 3, the addition of 1.0 equiv of HBF\(_4\cdot\)OE\(_2\) to acetonitrile solutions of 6 releases 2a and regenerates 4 (Scheme 2). The geometry around the metal center of 6 is close to octahedral, with the cyclopentadienyl ligand occupying three sites of a face. The reduction of the metal center as a consequence of its deprotonation has not any influence in the metalacyclopropene. Thus, the Os-C(1) and Os-C(2) bond lengths of 1.926(2) and 2.208(2) Å, respectively, are statistically identical to those of 5, whereas the chemical shifts for the C(1) (δ, 214.7) and C(2) (δ, -5.9) resonances in the \(^{13}\)C(\(^{1}\)H) NMR spectrum are also similar to those of 5.

In conclusion, an efficient osmium-catalyzed heterocyclization of o-(alkynyl)phenethylamines, which allows the easy preparation of a wide range of dopaminergic 3-benzazepines, has been discovered. The process takes place...
via osmacyclopropenes, which have been isolated and characterized by X-ray diffraction analysis.

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Keywords: benzazepines • cyclization • osmium catalysts • osmacyclopropenes • phenethylamines


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