

Osmium-Catalyzed 7-endo Heterocyclization of Aromatic Alkynols into Benzoxepines**

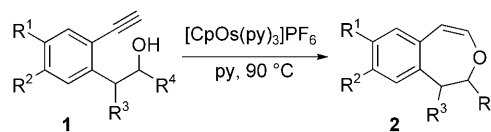
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Dedicated to Professor José Barluenga on the occasion of his 70th birthday

The development of effective strategies for the synthesis of heterocyclic compounds remains a very important challenge for modern organic synthesis.^[1] Molybdenum, tungsten, ruthenium, and rhodium complexes that afford vinylidene species have been among the most prominent catalytic precursors employed in their synthesis.^[2] The formation of dihydrofurans and dihydropyrans by catalytic heterocyclization with molybdenum- and tungsten vinylidenes has been pioneered by McDonald et al.,^[3] and later by Trost and Rhee using cationic ruthenium and rhodium complexes.^[4] More recently, the efficient preparation of indoles by the rhodium-catalyzed cycloisomerization of 2-(ethynyl)anilines,^[5] and the smooth preparation of benzofurans and benzopyrans by the ruthenium-catalyzed 5-endo and 6-endo heterocyclization reactions of substituted (2-ethynyl)phenols and benzylic alcohols, respectively, have been also described.^[6,7] On the other hand, the heterocyclization of alkynols into the seven-membered oxepines, a framework commonly found in complicated polycyclic marine natural products,^[8] has only been achieved from specific acetone-protected alkynol substrates via tungsten-vinylidene complexes.^[9]

Osmium is more reducing than ruthenium, prefers to be saturated by coordination, and redox isomers with more metal-carbon bonds.^[10] These characteristics have been argued to justify the versatility of stoichiometric osmium chemistry and its poorer catalytic activity in comparison with ruthenium.^[11] Herein, we report that osmium promotes catalysis more efficiently than ruthenium, tungsten, and

rhodium, promoting the 7-endo heterocyclization of aromatic alkynols into benzoxepines that have biological interest (Scheme 1).^[12]



Scheme 1. Osmium-catalyzed 7-endo heterocyclization reactions of aromatic alkynols.

Table 1 shows a series of complexes used for the heterocyclization of **1a** ($R^1, R^2, R^3 = H; R^4 = Me$) under several catalytic conditions. The tungsten complex $[W(=C(OMe)Me)(CO)_5]$ is a relatively poor catalyst for the regioselective 7-endo cyclization of **1a** into 3-benzoxepine **2a** (Table 1, entry 4).^[13] Moderate activities were achieved with ruthenium species $[CpRu(PPh_3)_2Cl]$ and $[CpRu(CH_3CN)_3]PF_6$ (Table 1, entries 6 and 8). The best results were obtained with osmium complexes $[Cp^N Os(CH_3CN)_2]PF_6$ ($Cp^N = CpCH_2CH_2NHMe$) and $[CpOs(py)_3]PF_6$ (Table 1, entries 9 and 10). Although rhodium has a high tendency to stabilize vinylidene compounds,^[14] poor catalytic activity was observed for the cyclization of **1a** into 3-benzoxepine **2a** (Table 1, entries 1 and 2).

A closer look at the 7-endo heterocyclization of **1b** ($R^1, R^3 = H; R^2, R^4 = Me$) with ruthenium and osmium complexes was then undertaken (Table 2). Regioselective 7-endo cyclization occurred on heating a pyridine solution of **1b** (0.15 M) in a sealed tube at 90 °C in the presence of 10 mol% $[CpRu(CH_3CN)_3]PF_6$ catalyst, giving a moderate yield of the 3-benzoxepine **2b** (Table 2, entry 1). Lower yields were obtained when either preformed or in-situ-formed $[CpRu(py)_3]PF_6$ was used (Table 2, entries 2 and 3). The use of ruthenium catalysts bearing Cp^N , a modified Cp ligand with a coordinating side arm, gave low yields, even after prolonged reaction times (Table 2, entries 4 and 5).^[15a] As expected from Table 1, more encouraging results were found using osmium catalysts. A good yield of **2b** was obtained in almost 24 hours when $[Cp^N Os(CH_3CN)_2]PF_6$ was used (Table 2, entry 6), and the reaction time could be reduced to only 3 hours when the catalyst was first heated in pyridine (Table 2, entry 7), which is mandatory for the cyclization to take place (Table 2, entry 8). Moreover, when the preformed $[Cp^N Os(py)_2]PF_6$ catalyst was employed, the yield increased

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Table 1: Heterocyclization of alkynol **1a** to 3-benzoxepine **2a**.^[a]

Entry	Catalyst (mol %)	Base	Solvent	T [°C]	t [h]	Yield of 2a [%] ^[b]
1	[{Rh(cod)Cl} ₂] (1)	(4-FC ₆ H ₄) ₃ P (4 mol %)	DMF	85	24	s.m.
2	[{Rh(cod)Cl} ₂] (5)	(4-FC ₆ H ₄) ₃ P (60 mol %)	DMF	85	10	(25)
3	[W{=C(OMe)Me}(CO) ₅] (10)	Et ₃ N	THF	60	24	s.m.
4	[W{=C(OMe)Me}(CO) ₅] (40)	Et ₃ N	THF	60	2	75 (50)
5	[W{=C(OMe)Me}(CO) ₅] (40)	py	THF	60	24	s.m.
6	[CpRu(PPh ₃) ₂ Cl] (10)	py	—	130	24	50 (29)
7	[(η ⁵ -indenyl)Ru(PPh ₃) ₂ Cl] (10)	py	—	90	24	s.m.
8	[CpRu(CH ₃ CN) ₃]PF ₆ (10)	py	—	90	1	64 (38)
9	[Cp ^N Os(CH ₃ CN) ₂]PF ₆ (10)	py	—	90	5	76 (62)
10	[CpOs(py) ₃]PF ₆ (10)	py	—	90	0.5	98 (65)

[a] [**1a**] = 0.15 M. [b] Yield determined by GC methods. Yield of isolated product given in parentheses. cod = 1,5-cyclooctadiene, Cp = cyclopentadienyl, s.m. = starting material, py = pyridine, DMF = N,N-dimethylformamide.

Table 2: 7-endo Heterocyclization of alkynol **1b** with [CpML₃]PF₆ and [Cp^NML₂]PF₆ catalysts.^[a]

Entry	M	Cp	L	t [h]	Yield of 2b [%] ^[b]
1	Ru	Cp	CH ₃ CN	1	54 (31)
2 ^[c]	Ru	Cp	CH ₃ CN	2	(15)
3	Ru	Cp	py	3	35 (19)
4	Ru	Cp ^N	CH ₃ CN	24	24 (21) ^[d]
5	Ru	Cp ^N	py	24	21 (20) ^[d]
6 ^[e]	Os	Cp ^N	CH ₃ CN	24	76 (53)
7 ^[c]	Os	Cp ^N	CH ₃ CN	3	(52)
8 ^[f]	Os	Cp ^N	CH ₃ CN	24	s.m.
9	Os	Cp ^N	py	3	82 (57)
10	Os	Cp	py	1	99 (68)
11 ^[g]	Os	Cp	py	5	98 (68)

[a] 10 mol % catalyst, [**1b**] = 0.15 M, py, 90 °C. [b] GC yields. Yield of isolated product given in parentheses. [c] 10 mol % catalyst was heated in pyridine for 1 hour before addition of **1b**. [d] Recovered **1b** (15–20%). [e] Heating at 110 °C. [f] [**1b**] = 0.15 M 1,2-dichloroethane. [g] 5 mol % osmium catalyst.

(Table 2, entry 9). To understand the difference between ruthenium and osmium, the heterocyclization of **1b** at 80 °C in the presence of [Cp^NM(py)₂]PF₆ (M = Ru, Os) was studied by ¹H and ¹³C{¹H} NMR spectroscopy. Whilst the osmium catalysts selectively afforded **2b**, the ruthenium analogue gave a complex mixture of organic products containing **2b**. The optimal conditions were found when [CpOs(py)₃]PF₆ was used, giving **2b** in excellent yields (Table 2, entries 10 and 11).^[15b]

Under the optimized conditions, a variety of aromatic alkynols **1** were converted into their corresponding 3-benzoxepines **2** in good yields (Table 3, entries 1–8). The electronic effects of substituents on the aromatic rings influenced the reaction kinetics, as shown by the faster reaction of electron-poor alkynol **1c** than electron-rich aromatic **1b** to give 3-benzoxepines **2b** and **2c**, respectively (30 versus 60 minutes; Table 3, entries 2 and 3). Other secondary alkynols, such as benzylic alkynol **1d**, cyclohexanol derivative **1e**, the parent and electron-rich primary alkynols **1f** and **1g**, and even tertiary alkynol **1h** all smoothly afforded their corresponding 3-benzoxepines in times ranging from 30–90 minutes (Table 3,

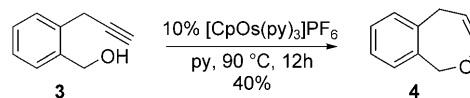
entries 4–8). However, nonterminal alkynol **1i** failed to cyclize with either ruthenium or osmium catalysts, indicating that the cyclization occurs via a catalytic metal–vinylidene complex.^[2,11d]

The superior capacity of [CpOs(py)₃]PF₆ as the catalyst for this reaction is also shown in the challenging regioselective 7-endo heterocyclization of benzylic-type alkynol **3**. The pharmacologically interesting 2-benzoxepine **4**^[12] can be isolated in 40 % yield after 12 hours at 90 °C (Scheme 2). Under the same conditions, the ruthenium counterpart was totally inactive, as

Table 3: Osmium-catalyzed 7-endo heterocyclization of aromatic alkynols **1** into 3-benzoxepines **2**.^[a]

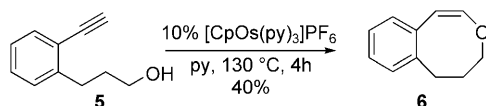
Entry	Alkynol 1	3-Benzoxepine 2	Yield [%] ^[b]
1			65
2			68
3			63
4			58
5			56
6			60
7			60
8			69
9 ^[c]			s.m.

[a] Typical conditions: 10 mol % [CpOs(py)₃]PF₆, 0.15 M, pyridine, 90 °C, 0.5–1.5 hours. [b] Yield of isolated product. [c] 10 mol % [CpRu(CH₃CN)₃]PF₆, 0.15 M, py, 90 °C. s.m. = starting material.


Scheme 2. Osmium-catalyzed 7-endo heterocyclization of benzylic-type alkynol **3** to 2-benzoxepine **4**.

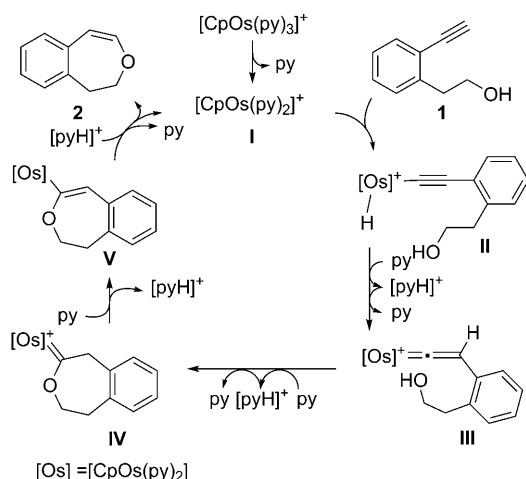
was $[\text{Rh}(\text{cod})\text{Cl}]_2$ and $[\text{W}\{\text{C}(\text{OMe})\text{Me}\}(\text{CO})_5]$ (for reaction conditions, see Table 1).^[16]

Interestingly, even the more challenging regioselective osmium-catalyzed 8-*endo* heterocyclization of aromatic alkynol **5** into 3-benzo[*d*]oxocine **6** was successfully achieved and the product was isolated in moderate yield (40 %), although in this case the reaction did not proceed as cleanly (monitored by GC methods) and harsher conditions were necessary (Scheme 3).^[17]



Scheme 3. Osmium-catalyzed 8-*endo* heterocyclization of aromatic alkynol **5** to 3-benzo[*d*]oxocine **6**.

These heterocyclization reactions can be rationalized according to the mechanism in Scheme 4. After dissociation of py from the osmium precursor, unsaturated 16e[−] species **I**



Scheme 4. Proposed catalytic cycle for the osmium-catalyzed heterocyclization.

should be formed. Facile oxidative addition of the C(sp)–H bond of the terminal alkyne to the metal center could afford hydride–Os^{IV}–alkynyl intermediates **II**.^[18] Removal of the hydride as a proton by pyridine followed by re-protonation at the C_β atom would afford the osmium–vinylidenes **III**.^[18,19] Then, the α-electrophilic^[2a,20] center of the vinylidene could be susceptible to intramolecular attack by the alcohol to give the 2-oxacycloalkylidene osmium intermediates **IV**,^[21] which, in the presence of py would afford vinylic osmium species **V**.^[22] A related sequence has been proposed for the formation of lactones from carboxylic acids that contain a triple bond in the presence of catalytic amounts of a TpRu complex (Tp = hydrotris(pyrazolyl)borate).^[23] Finally, protonolysis of the heterocyclic ligand would liberate the 3-benzoxepine **2** and regenerate **I**.

In conclusion, osmium complexes are more efficient catalysts than tungsten, ruthenium, and rhodium systems for

the regioselective 7-*endo* heterocyclization of aromatic alkynols into benzoxepines, suggesting that osmium can be a promising alternative to the classical metal catalysts for these reactions.^[24] Additionally, the challenging regioselective 8-*endo* heterocyclization of an aromatic alkynol could also be achieved with osmium catalysts. Further studies to expand the scope of these reactions are in progress.

Experimental Section

Typical experimental procedure: A mixture of **1b** (50 mg, 0.29 mmol) and $[\text{CpOs}(\text{py})_3]\text{PF}_6$ (0.018 mg, 0.029 mmol) in pyridine (2.0 mL) was stirred in a sealed tube under argon for 1 hour at 90 °C (monitored by GCMS). The reaction mixture was then cooled to room temperature and extracted from saturated aqueous NH_4Cl (2 mL) with diethyl ether (3 × 2 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 , filtered, and evaporated in vacuo. Purification by flash column chromatography on silica gel using a gradient diethyl ether/*n*-hexane (0.1:9.9 to 1:9) gave 3-benzoxepine **2b** (34 mg, 68 %) as a yellowish oil. ¹H NMR (300 MHz, CDCl_3), δ = 6.98–6.90 (m, 2H), 6.83 (s, 1H), 6.30 (d, *J* = 8.1 Hz, 1H), 5.31 (d, *J* = 8.1 Hz, 1H), 4.27–4.18 (m, 1H), 2.94 (d, *J* = 3.8 Hz, 2H), 2.27 (s, 3H), 1.34 ppm (d, *J* = 6.4 Hz, 3H). ¹³C NMR, DEPT (75 MHz, CDCl_3), δ = 143.3 (CH), 137.3 (C), 134.9 (C), 132.4 (C), 129.6 (CH), 128.6 (CH), 127.0 (CH), 104.5 (CH), 75.9 (CH), 44.7 (CH₂), 21.6 (CH₃), 20.9 ppm (CH₃). MS, *m/z* (% relative intensity): 175 ($[\text{M} + \text{H}]^+$, 100), 157 (79), 145 (31), 131 (20). HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$: 175.1123; found: 175.1117.

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