Heterocyclization

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

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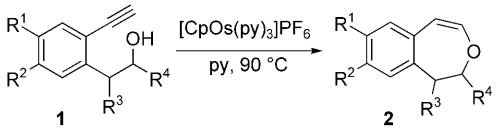
Dedicated to Professor José Barluenga on the occasion of his 70th birthday

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 acetonide-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 [$Cp^NOs(CH_3CN)_2$]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 reactions 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 [$Cp^NOs(CH_3CN)_2$]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 [$Cp^NOs(py)_2$]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)	$(4\text{-}FC_6H_4)_3P$ (4 mol%)	DMF	85	24	s.m.
2	$[\{Rh(cod)Cl\}_2]$ (5)	$(4\text{-}FC_6H_4)_3P$ (60 mol%)	DMF	85	10	(25)
3	$[W\{=C(OMe)Me\}(CO)_5]$ (10)	Et_3N	THF	60	24	s.m.
4	$[W\{=C(OMe)Me\}(CO)_5]$ (40)	Et_3N	THF	60	2	75(50)
5	$[W\{=C(OMe)Me\}(CO)_5]$ (40)	py	THF	60	24	s.m.
6	$[CpRu(PPh_3)_2Cl]$ (10)	py	–	130	24	50(29)
7	$[(\eta^5\text{-indenyl})Ru(PPh_3)_2Cl]$ (10)	py	–	90	24	s.m.
8	$[CpRu(CH_3CN)_3]PF_6$ (10)	py	–	90	1	64(38)
9	$[Cp^NOs(CH_3CN)_2]PF_6$ (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 $[CpML_3]PF_6$ and $[Cp^NML_2]PF_6$ catalysts.[a]

Entry	M	Cp	L	*t* [h]	Yield of **2b** [%][b]
1	Ru	Cp	CH_3CN	1	54 (31)
2[c]	Ru	Cp	CH_3CN	2	(15)
3	Ru	Cp	py	3	35 (19)
4	Ru	Cp^N	CH_3CN	24	24 (21)[d]
5	Ru	Cp^N	py	24	21 (20)[d]
6[e]	Os	Cp^N	CH_3CN	24	76 (53)
7[c]	Os	Cp^N	CH_3CN	3	(52)
8[f]	Os	Cp^N	CH_3CN	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)

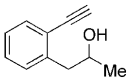
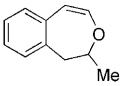
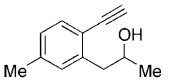
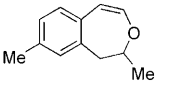
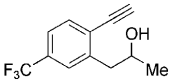
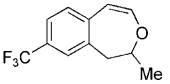
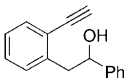
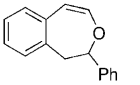
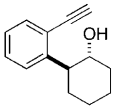
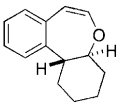
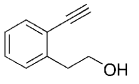
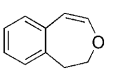
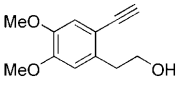
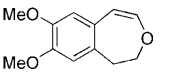
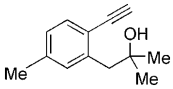
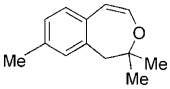
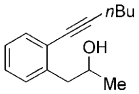
[a] 10 mol% catalyst, [**1b**] = 0.15 M, py, 90°C. [b] GC yields. Yield of isolated product given in parentheses. [c] 10 mol% catalyst was heated in pyridine for 1 hour before addition of **1b**. [d] Recovered **1b** (15–20%). [e] Heating at 110°C. [f] [**1b**] = 0.15 M 1,2-dichloroethane. [g] 5 mol% 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 $[Cp^NM(py)_2]PF_6$ (M = Ru, Os) was studied by ^1H and $^{13}C\{^1H\}$ 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 $[CpOs(py)_3]PF_6$ was used, giving **2b** in excellent yields (Table 2, entries 10 and 11).[15b]

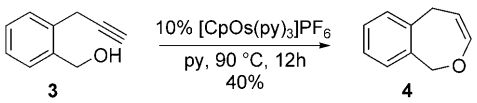
Under the optimized conditions, a variety of aromatic alkynols **1** were converted into their corresponding 3-benzoxepines **2** in good yields (Table 3, entries 1–8). The electronic effects of substituents on the aromatic rings influenced the reaction kinetics, as shown by the faster reaction of electron-poor 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 $[CpOs(py)_3]PF_6$ 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		**1a**		**2a**	65
2		**1b**		**2b**	68
3		**1c**		**2c**	63
4		**1d**		**2d**	58
5		**1e**		**2e**	56
6		**1f**		**2f**	60
7		**1g**		**2g**	60
8		**1h**		**2h**	69
9[c]		**1i**			s.m.

[a] Typical conditions: 10 mol% $[CpOs(py)_3]PF_6$, 0.15 M, pyridine, 90°C, 0.5–1.5 hours. [b] Yield of isolated product. [c] 10 mol% $[CpRu(CH_3CN)_3]PF_6$, 0.15 M, py, 90°C. s.m. = starting material.

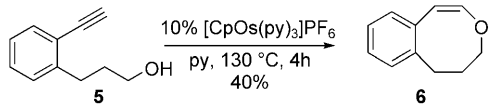


3 4

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

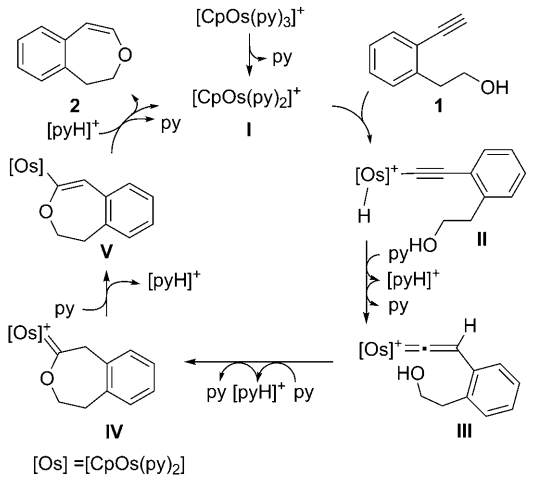
was $[Rh(cod)Cl]_2$ and $[W\{=C(OMe)Me\}(CO)_5]$ (for reaction conditions, see Table 1).[16]

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 $[CpOs(py)_3]PF_6$ (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. ^{1}H NMR (300 MHz, $CDCl_3$), $\delta = 6.98$–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). ^{13}C NMR, DEPT (75 MHz, $CDCl_3$), $\delta = 143.3$ (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 (CH_2), 21.6 (CH_3), 20.9 ppm (CH_3). MS, *m*/*z* (% relative intensity): 175 ($[M+H]^+$, 100), 157 (79), 145 (31), 131 (20). HRMS (ESI) calculated for $C_{12}H_{15}O$ $[M+H]^+$: 175.1123; found: 175.1117.

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[15] a) Metal $[Cp^{N}M(py)_2]PF_6$ complexes in pyridine are in equilibrium with $[Cp^{N}M(py)_3]PF_6$ (M = Ru, Os) that contain a free pendant group. For thermodynamic data of these equilibria, and b) for kinetic data of the formation of **2b**, see the Supporting Information.

[16] a) Smooth 6-*exo* cyclization occurred at room temperature with 1% $PtCl_2$ (80% yield); for details, see the Supporting Information. b) For alkynols **1**, smooth 6-*exo* cyclization followed by dimerization was observed.

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