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Oxidative Cyclization of 1,5-Dienes with Hydrogen Peroxide Catalyzed by an Osmium(III) Complex: Synthesis of *cis*-Tetrahydrofurans

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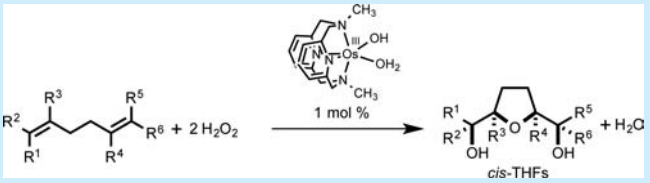
Supporting Information

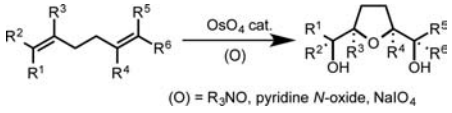
ABSTRACT: Stereoselective oxidative cyclization of 1,5-dienes with hydrogen peroxide catalyzed by $[Os^{III}(OH)(H_2O)(L{-}N_4Me_2)](PF_6)_2$ (**1**: $L{-}N_4Me_2$ = *N*,*N*′-dimethyl-2,11-diaza-[3,3](2,6)pyridinophane) is explored. 1,5-Dienes involving geraniol derivatives are converted to the corresponding tetrahydrofurans in modest to high yields. The products exclusively have the *cis*-conformation with respect to the substituents at the 2- and 5-positions of the tetrahydrofuran ring. The products also have a *syn*-conformation with respect to the furan oxygen atom and the hydroxyl groups. Mechanistic studies including a direct reaction of the oxo-hydroxo-osmium(V) complex, **2**, with a dihydroxylated geraniol derivative are performed.



In recent years, there has been a drive to develop catalysts that work with high atom economy and selectivity, but which also have a broad substrate scope. Since nearly 80% of all reactions performed in the chemical industry are oxidations or reductions, the most atom economically attractive and environmentally friendly oxidation reagents for bulk oxidation processes are molecular oxygen (O_2) or hydrogen peroxide (H_2O_2).

The substituted tetrahydrofurans (THFs) are frequently found in a wide range of natural products and biogenetically intriguing polyoxygenated cytotoxic molecules. Since these compounds have potentially cytotoxic activities against cancer cells, multidrug resistant tumors, and significant bioactivities including antiparasitics, antimalarial, and pesticidal activities, numerous synthetic approaches to this structural unit have been made.[1−8] Among the reported procedures, the most established method to construct THFs in a single step is the oxidative cyclization of 1,5-dienes using the OsO_4 catalyst.[6,9] The OsO_4-catalyzed methods selectively afford *cis*-THFs with respect to the orientation of the substituents at the 2- and 5-positions (Scheme 1).[6,9−16] However, these methods have some disadvantages such as (1) the use of an excess amount of the strong reoxidant such as $NaIO_4$ and tertiary amine-*N*-oxide,[6,9,11−13] (2) requirement of highly acidic conditions,[14,15] and (3) byproduct formation generated from the re-oxidants. So far, there has been no report on the re-oxidation reaction of the reduced forms of the catalyst (OsO_4) by O_2 or H_2O_2 in the oxidative cyclization of 1,5-dienes. This may be due to the high energy barrier for oxygen atom transfer oxidation of the reduced catalyst to regenerate OsO_4.

Scheme 1. Stereoselective Formation of *cis*-Tetrahydrofurans



Our strategy for developing a new class of catalysts to oxygenate alkenes with O_2 or H_2O_2 is based on the synthesis of osmium analogues of the active oxidant of Rieske dioxygenase iron enzyme that catalyzes *cis*-selective arene dihydroxylation with O_2 or H_2O_2, using an oxo-hydroxo-iron(V) species as an active oxidant (Figure 1, left).[17,18] Recently, we have developed the oxido-hydroxido-osmium(V) complexes supported by a tripodal tetradentate ligand TPA (tris(2-pyridylmethyl)amine) or a macrocyclic tetradentate ligand $L{-}N_4Me_2$ (*N*,*N*′-dimethyl-2,11-diaza[3.3](2,6)pyridinophane),[19,20] which are capable of

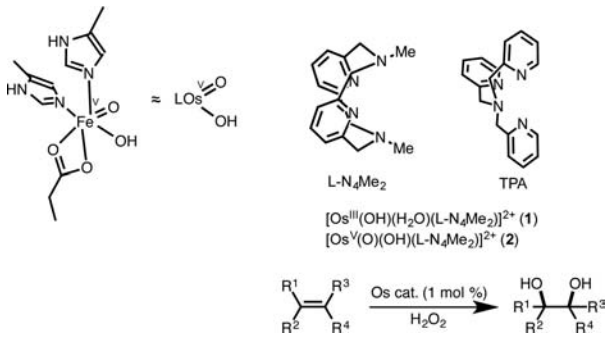


Figure 1. (Left) Active oxidant of Rieske dioxygenase and (right) bioinspired osmium model complexes, and the catalytic dihydroxylation of alkenes with H_2O_2.

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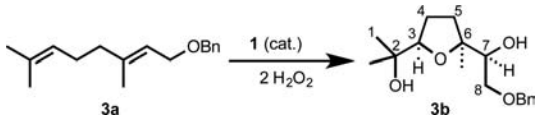
performing very efficient catalytic *cis*-dihydroxylation of various alkenes using H_2O_2 as the terminal oxidant (Figure 1, right). The osmium(V) complexes are regenerated from the hydroxido-aquo-osmium(III) complexes and H_2O_2. Thus, if the Os(V)/Os(III) redox cycle is carried out twice in a 1,5-diene oxidation, a new protocol for oxidative cyclization of 1,5-dienes will be constructed, using environmentally benign H_2O_2 as a terminal oxidant. In this study, we have employed $[Os^{III}(OH)(OH_2)(L{-}N_4Me_2)](PF_6)_2$ (**1**) as a precursor complex for the active oxidant $[Os^{V}(O)(OH)(L{-}N_4Me_2)](PF_6)_2$ (**2**) to develop an efficient catalytic oxidative cyclization of 1,5-dienes using H_2O_2.

At first, oxidation of benzyl geranyl ether (**3a**) with H_2O_2 as a terminal oxidant under catalytic conditions was examined. Slow addition of 2 equiv of H_2O_2 (30% aqueous solution) using a syringe pump to a pH 4.0 H_2O (2.5 mL)/*t*-BuOH (2.5 mL) solution containing the substrate (0.5 mmol) and a catalytic amount of **1** (1 mol %) at 70 °C for 5 h gave a tetrahydrofuran derivative **3b** in a 25% yield (see Supporting Information). The *cis*-configuration of the product **3b** was confirmed by comparison with the ^1H and ^{13}C NMR spectra of the authentic sample reported in the literature[16] and by the NOESY spectrum (Figure S1). With respect to the orientation of the C6−O bond of the furan ring and C7−OH bond of **3b**, a *threo* structure was determined. Then, the catalytic oxidation was carried out at pH 2.1, 4.0, 6.8, and 10.0 (Table 1). The

Table 1. Optimization of Reaction Conditions for the Oxidative Cyclization of 3a to 3b[a]



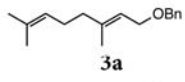
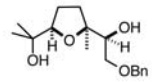
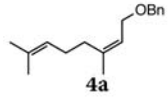
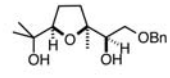
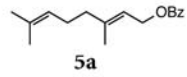
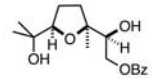
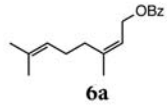
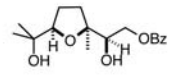
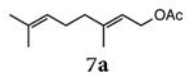
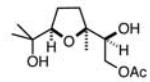
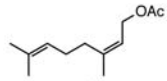
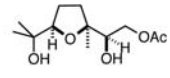
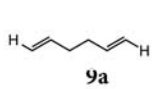
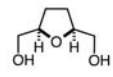
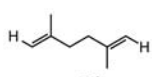
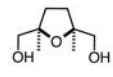
entry	cat. (mol %)	pH	time, h	yield, %[b]
1	**1** (1)	2.1[c]	5	22
2	**1** (1)	4.0[d]	5	25
3	**1** (1)	6.8[e]	5	48
4	**1** (1)	10.0[f]	5	0
5	**1** (1)	6.8[e]	3	23
6	**1** (1)	6.8[e]	7	41
7	**1** (2)	6.8[e]	5	59
8	**1** (3)	6.8[e]	5	48
9	$K_2[OsO_2(OH)_4]$ (1)	6.8[e]	5	trace

[a]Reaction conditions: cat. (1−3 mol %), **3a** (500 μmol), and H_2O_2 (1000 μmol) in a buffer solution (H_2O/*t*-BuOH (2.5 mL/2.5 mL) at 70 °C. [b]^1H NMR yield. [c]$C_6H_4(COOH)(COOK)$/HCl. [d]CH_3COOH/CH_3COONa. [e]KH_2PO_4/Na_2HPO_4. [f]Na_2CO_3/$NaHCO_3$.

oxidative cyclization proceeded most efficiently at nearly neutral pH conditions (pH 6.8, entry 3, 48%). The yield of **3b** decreased at the lower pH conditions (25% at pH 4.0 and 22% at pH 2.1), whereas the oxidative cyclization did not proceed at all at higher pH 10.0, and the substrate was recovered instead (entries 2, 1, and 4). On the other hand, when the reaction time was shortened or prolonged from 5 to 3 h or to 7 h, respectively, the yield decreased in both cases (entries 5 and 6). Increase of the loaded amount of catalyst from 1 mol % to 2 and 3 mol % did not result in significant improvement of the yield of **3b** (entries 7 and 8). Under the optimized conditions (entry 3, Table 1), most of the starting material, 1,5-diene (**3a**), was consumed and some byproducts such as the C-7 ketone derivative of **3b** (overoxidation product) was detected. This is a reason for suppression of the yield of desired product **3b**.[21]

Control experiments were performed in the oxidation of the substrate with H_2O_2 using $K_2[OsO_2(OH)_4]$ under the same conditions. In this case, only a trace of amount of **3b** was obtained (entry 9). It should be also noted that the oxidation of **3a** using NMO (*N*-methylmorpholine *N*-oxide) yielded *cis*-dihydroxy-5-alkene under the present conditions as reported in the literature.[22] The above-mentioned results demonstrate that the present Os-complex **1** is a unique catalyst for selective transformation of 1,5-dienes to *cis*-THFs with H_2O_2. The oxidative cyclization of other geraniol derivatives under the same conditions used for the reaction shown in entry 3 in Table 1 was carried out (Table 2).

Table 2. Oxidative Cyclization of 1,5-Dienes with H_2O_2 Catalyzed by 1[a]

entry	substrate	product		yield, %[b]
1	 **3a**		**3b**	48
2	 **4a**		**4b**	42
3	 **5a**		**5b**	30
4	 **6a**		**6b**	23
5	 **7a**		**7b**	40
6	 **8a**		**8b**	32
7	 **9a**		**9b**	33
8	 **10a**		**10b**	42

[a]Experimental conditions are the same as those for entry 3 in Table 1. [b]^1H NMR yield.

In all the cases, the corresponding *cis*-THF products were obtained in modest yields, and the yields of the products obtained from the *E*-isomers were higher than those obtained from the corresponding *Z*-isomers (entries 1 vs 2, 3 vs 4, and 5 vs 6). The yield of product was decreased, when the benzyl-ether group (OBn) was changed to an acetoxy (OAc) group. The simple 1,5-hexadienes without the oxy group were also converted selectively to the tetrahydrofuran derivatives having a *cis-syn* structure (entries 7 and 8). On the other hand, when a cyclic 1,5-diene such as a cyclooctadiene was employed as a substrate, the corresponding tetrahydrofuran derivative was not

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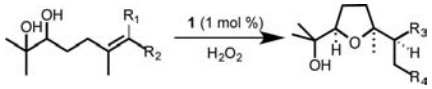
obtained at all, but the *cis*-diol product was obtained instead (not shown in Table 2).

To gain insight into the mechanism for the catalytic oxidative cyclization of 1,5-dienes, *cis*-1,2-dihydroxy-5,6-alkenes, **3c**, **4c**, **7c**, and **8c**, were employed as substrates to see whether the corresponding tetrahydrofuran derivatives can be formed (Table 3), since complex **1** worked as a catalyst for *cis*-1,2-dihydroxylation of alkenes.[20] As a result, the corresponding tetrahydrofuran derivatives adopting a *cis-syn* structure were obtained in modest yields, indicating that the *cis*-dihydroxy-5,6-alkenes are involved in the catalytic cycle. Namely, the employed 1,5-dienes may initially be converted to the *cis*-1,2-dihydroxy-5,6-alkenes as the precursors of the THF products. In these cases as well, the yields of products obtained from the (*E*) isomers were higher than those obtained from their (*Z*) isomers (entries 1 and 3 vs 2 and 4). The product yields from the dihydroxy-5,6-alkenes were lower than those obtained directly from the corresponding 1,5-dienes. The result may suggest that the oxidative cyclization proceeds on the osmium center and coordination of the added *cis*-1,2-dihydroxy-5,6-alkene to the osmium center is rather slow. Thus, the added alkene undergoes overoxidation with H_2O_2 before the coordination to the osmium center. In fact, a reaction of **3c** with H_2O_2 in the absence of the catalyst in *t*-BuOH buffer (pH 6.8) at 70 °C gave a complicated mixture of overoxidation products. Then, a direct reaction of the oxido-hydroxido-Os(V) complex, $[Os^{V}(O)(OH)(L{-}N_4Me_2)](PF_6)_2$ (**2**), with dihydroxy-5,6-alkene was examined (Figure 2, top), since **2** is an active oxidant for alkene dihydroxylation.[20] The treatment of **2** (10 mol % 50 μmol) with dihydroxy-5,6-alkenes (**3c**) (500 μmol) in *t*-BuOH (1.5 mL)/H_2O (3.5 mL) at 70 °C for 5 h gave the corresponding tetrahydrofuran derivative (**3b**) in a 30% yield based on **2** (see Supporting Information). The result indicates that the diol substrate **3c** can bind to the oxido-hydroxido-Os(V) complex **2** and, then, oxidative cyclization proceeds to give **3b** in the osmium coordination sphere. Furthermore, when a reaction of **2** with 10 equiv of **3c** in H_2O was monitored by UV–vis spectroscopy (Figure 2, below), the spectrum of **2** changed to that of **1** as the reaction proceeded,[20] from the final solution of which **3b** was detected by HPLC analysis. Based on the above-mentioned results, a catalytic mechanism is deduced as shown in Scheme 2. At first, H_2O_2 oxidizes the starting complex $[Os^{III}(OH)(H_2O)(L)]^{2+}$ (**1**) to generate an active oxidant $[Os^{V}(O)(OH)(L)]^{2+}$ (**2**), which binds to a 1,5-diene in a [3 + 2] cycloaddition manner to produce the *cis*-dihydroxy-5,6-alkene and the osmium(III) complex **1**. The complex **1** is reoxidized by H_2O_2 to regenerate an active oxidant **2**. Then, complex **2** binds to the vicinal diol–alkene to give an Os(V) intermediate A, where the hydroxo group of **2** is replaced with the one of the hydroxy group of the vicinal diol–alkene. Then the remaining alkene moiety is oxidized to yield an intermediate **B** consisting of an osmium(III) complex and the product. By the subsequent hydrolysis, the starting **1** and the tetrahydrofuran having a *cis-syn* structure are produced.

Finally, we examined chelate ligand effects on the catalytic performance of the osmium complex. A hydroxido-aquo-osmium(III) complex coordinated by two 2,2′-bipyridyl (bpy) ligands, $[Os^{III}(OH)(H_2O)(bpy)_2](CF_3SO_3)_2$ (**9**), was synthesized. The X-ray diffraction experiments of the single crystal revealed that the osmium(III) center of **9** has a distorted octahedral geometry similar to those coordinated by TPA and $L{-}N_4Me_2$ (Figure S18). Although **9** catalyzed the oxidative cyclization of **3**, **4**, **7**, and **8** with H_2O_2 to yield the corresponding *cis-syn*-THFs, the product yields were lower as compared with those by **1** (33% for **3b**, 28% for **4b**, 25% for **7b**, and 24% for **8b**). This is probably due to the weak chelating effect of the bidentate bpy ligand compared to those of the tetradentate $L{-}N_4Me_2$ ligand, resulting in the lower stability of **9**.

In summary, we have demonstrated that *cis*-hydroxido-aquo-osmium(III) complexes (**1**) supported by a macrocyclic

Table 3. Oxidative Cyclization of *cis*-1,2-Dihydroxy-5,6-alkenes with H_2O_2 Catalyzed by 1[a]



entry	substrate	product	yield, %[a]
1	**3c**, R_1 = H, R_2 = CH_2OBn	**3b**	33
2	**4c**, R_1 = CH_2OBn, R_2 = H	**4b**	28
3	**7c**, R_1 = H, R_2 = CH_2OAc	**7b**	30
4	**8c**, R_1 = CH_2OAc, R_2 = H	**8b**	16

[a] ^{1}H NMR yield.

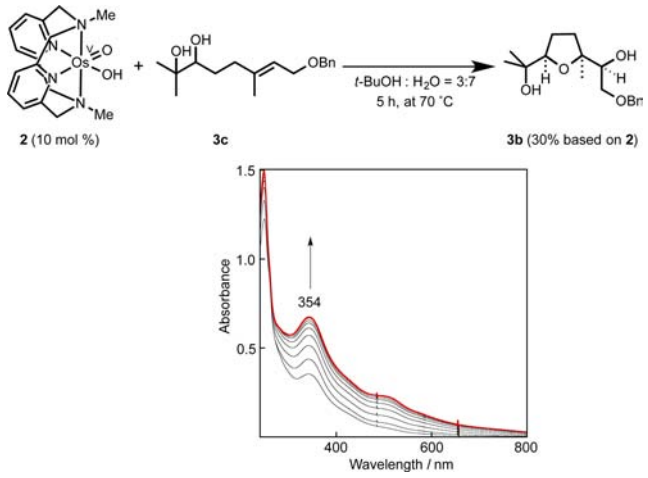
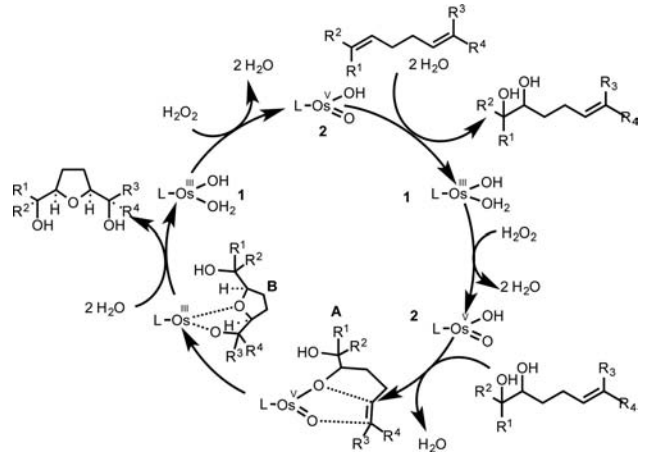


Figure 2. (Top) Direct reaction of **2** (50 μmol) with **3c** (500 μmol) on a preparative scale. (Bottom) UV–vis spectral changes observed upon treatment of **2** (0.1 mM) with **3c** (1.0 mM) in H_2O.

Scheme 2. Proposed Mechanism for Oxidative Cyclization of 1,5-Dienes with H_2O_2 Catalyzed by 1



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tetradentate ligand L–N_4Me_2 (*N*,*N*′-dimethyl-2,11-diaza[3.3]-(2,6)pyridinophane) can catalyze the stereoselective oxidative cyclization of 1,5-dienes to give tetrahydrofuran derivatives with *cis-syn* conformation in modest to high yields using H_2O_2 as the terminal oxidant in an aqueous media. Furthermore, this reaction exhibits an atom efficiency of 74%[23] and is regarded as being environmentally friendly.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00064.

General experimental procedures and characterization data (PDF)

Crystallographic data for **9** (CIF)

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Notes

The authors declare no competing financial interest.

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