

The OsO₄-mediated oxidative cleavage of olefins catalyzed by alternative osmium sources

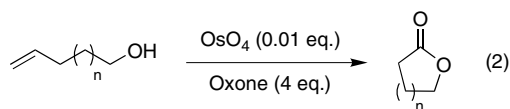
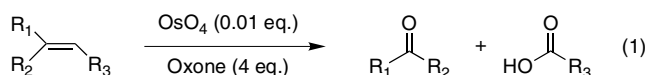
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Received 28 January 2006; revised 11 March 2006; accepted 14 March 2006

Abstract—The OsO₄-mediated oxidative cleavage of olefins is compatible with alternative, easier-to-handle osmium sources. Four different osmium sources were employed with favorable results.
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Recently, we reported on an osmium tetroxide-promoted catalytic oxidative cleavage of olefins.¹ This reaction employs a catalytic portion of osmium tetroxide in conjunction with several equivalents of Oxone as a co-oxidant to effect the cleavage of a variety of olefins (Scheme 1, Eq. 1). For mono- and vicinal disubstituted alkenes, this methodology provides easy access to the corresponding carboxylic acid cleavage products. Higher order alkenes (or geminal disubstituted olefins) grant access to the corresponding ketones. The reactions usually proceed in excellent yields for the cleavage of a number of different alkene substrates. The oxidative methodology was extended to include the direct formation of lactones by way of the oxidative cleavage of alkenols (Scheme 1, Eq. 2).² This transformation was highlighted during the efficient total synthesis of (+)-tanikolide.³



Scheme 1. Osmium mediated oxidative cleavage/oxidative lactonization.

Keywords: Osmium tetroxide; Oxidative cleavage; Oxone; Oxidative lactonization.

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Given the apparent success of this methodology, we set out to explore the use of alternate sources of the osmium catalyst. Namely, we present herein an investigation of the integrity of this methodology when cheaper, less toxic, and easier-to-handle osmium sources are employed. Four different sources of osmium were chosen for this study, each offering its own advantages over osmium tetroxide. Both osmium trichloride and potassium osmate are cheaper, less volatile osmium sources, which can be handled safely in their solid state, a considerable advantage to preparing organic solutions of osmium tetroxide. Commercially available polymer-bound osmium tetroxide (1 wt % on poly(4-vinylpyridine))^{4,5} also provides a catalyst source that is easier to handle and less volatile than standard samples of osmium tetroxide. A final osmium source, OsEnCat™, was kindly provided by the Ley laboratory. OsEnCat™ is osmium tetroxide that has been microencapsulated in polyurea microcapsules.^{6,7} The Ley group has shown that this catalyst system is highly effective in both the catalytic dihydroxylation of olefins under Upjohn conditions⁸ and in the oxidative cleavage of olefins by the Lemieux–Johnson reaction.^{9,10} This particular osmium source offers the intriguing opportunity of recycling the catalyst for use in subsequent reactions. Ley and co-workers have shown that a sample of OsEnCat™ can be used for five iterations without any detectable leaching of osmium tetroxide or loss of catalytic activity.

Each of the four sources of osmium was screened for activity in the oxidative cleavage and oxidative lactonization reactions.¹¹ The reactions were carried out for 12 h using a 0.1 M solution of substrate in DMF, with 4 equiv of Oxone and 0.01 equiv of catalyst when

osmium trichloride or potassium osmate was employed. A lower catalyst loading of 0.001 equiv of polymer-bound and 0.0025 equiv of encapsulated osmium tetroxide was used for some substrates in order to avoid adding an impractically large mass of substance to achieve the desired catalyst loading. Other substrates, however, proved too sluggish when the lower catalyst loading was used. So for those substrates, the use of 0.01 equiv of either polymer-bound osmium tetroxide or OsEnCat™ is recommended. Control experiments with 0.01 equiv of osmium tetroxide were run for comparisons. The results from this study are given in Table 1.

Entries 1 and 2 showcase the ability of each osmium source to efficiently cleave both aromatic and aliphatic olefins. Cinnamic acid (entry 3) serves as an example of an electron deficient system. All osmium sources performed on a comparable level with osmium tetroxide, but 0.01 equiv of both polymer-bound osmium tetroxide and OsEnCat™ were needed to efficiently promote cleavage.

The cleavage of α -methylstyrene gave the desired acetophenone cleavage product with all five sources of osmium in yields ranging from 71% to 95% (entry 4). In each case, however, the acetophenone product was

contaminated with other oxidation products (vide infra). Entries 5 and 6 highlight the ability of this methodology to efficiently effect the oxidative cleavage of higher order olefins. As described previously,¹ the use of sodium bicarbonate (4 equiv) as an additive is necessary to suppress side reactions.

The sluggish oxidation of phenyl acetylene under the prescribed reaction conditions (entry 7: only 8–42% yield of benzoic acid after 24 h) suggested that one might be able to garner some selectivity for the cleavage of olefins in the presence of alkynes. To test this hypothesis, an ene-yne substrate (see Table 1, entry 8) was prepared and subjected to the standard conditions. The facile cleavage of the olefin, while preserving the alkyne, was achieved with each of the five osmium sources. This selectivity, coupled with the immunity of other sensitive functionalities such as alcohols and vicinal diols, makes this methodology an attractive strategy for the oxidative cleavage of olefins within highly functionalized intermediates.

With the final entry in Table 1, the alternative forms of osmium tetroxide were utilized for the oxidative lactonization protocol. The alkenol depicted in entry 9 was readily prepared by TBAF deprotection of the previously reported O-silylated precursor.² Treatment with

Table 1. Osmium mediated oxidative cleavage with alternative osmium sources

Entry	Substrate	Product	OsCl ₃ (%)	K ₂ OsO ₄ ·2H ₂ O (%)	P.B. OsO ₄ (%)	OsEnCat (%)	OsO ₄ (%)
1 ^{a,b}		PhCO ₂ H	84	84	80	79	84
2			100	96	100	75	97
3		PhCO ₂ H	84	79	30, 96 ^c	96 ^c	74
4 ^{d,e}			90	95	82	71	84
5		PhCO ₂ H	96	67	79 ^c	55	88
6			97	85	91 ^c	97 ^c	82
7		PhCO ₂ H	21	38	16	8	42
8			76	82	48, 93 ^c	51, 95 ^c	75
9			98	93	95 ^c	95 ^c	98

^a Reactions were carried out using a 0.1 M solution of substrate in DMF with 0.01 equiv of osmium source when OsCl₃ or K₂OsO₄·2H₂O was used or 0.001 equiv when Polymer-bound OsO₄ was used or 0.0025 equiv when OsEnCat™ was used, and 4 equiv of Oxone, and 4 equiv of sodium bicarbonate (entries 5 and 6 only). Reactions were run at room temperature overnight.

^b All yields are isolated yields unless otherwise specified.

^c 0.01 equiv of either polymer-bound OsO₄ or OsEnCat™ was employed.

^d GC yield.

^e Diol and acid products also formed (vide infra).


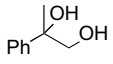
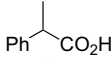
the oxidative reaction conditions described above, generated in all cases the desired lactone product in excellent yields (93–98% yield).

As mentioned above the presence of other oxidative side products in the cleavage of α -methylstyrene warrants some comment. For all five osmium sources (Table 1, entry 4), the cleavage of this substrate produced predominantly the desired acetophenone (**1**) cleavage product. We were surprised, however, to see evidence for the dihydroxylation product, 2-phenyl-1,2-propanediol (**2**), along with 2-phenylpropanoic acid (**3**) and acetophenone. In order to verify the presence of these two side products in the ^1H NMR spectrum and GC traces, the diol and carboxylic acid products were prepared independently (the diol via OsO_4 -mediated dihydroxylation under Upjohn conditions and the acid by Oxone-mediated oxidation of the aldehyde). With pure samples of the two byproducts in hand, their presence in the crude ^1H NMR spectra and GC traces of the cleavage reaction for α -methylstyrene was verified. GC analysis of the reaction products obtained from the cleavage reaction for each of the five osmium sources is listed in Table 2.

The presence of diol **2**, resulting from hydrolysis of the osmate ester, was minimal regardless of the osmium source. The presence of 2-phenylpropanoic acid (**3**), however, varied depending on the osmium source, with as little as 3% formed when potassium osmate was employed to 26% when OsEnCatTM was used. It is interesting to speculate about the origin of this particular

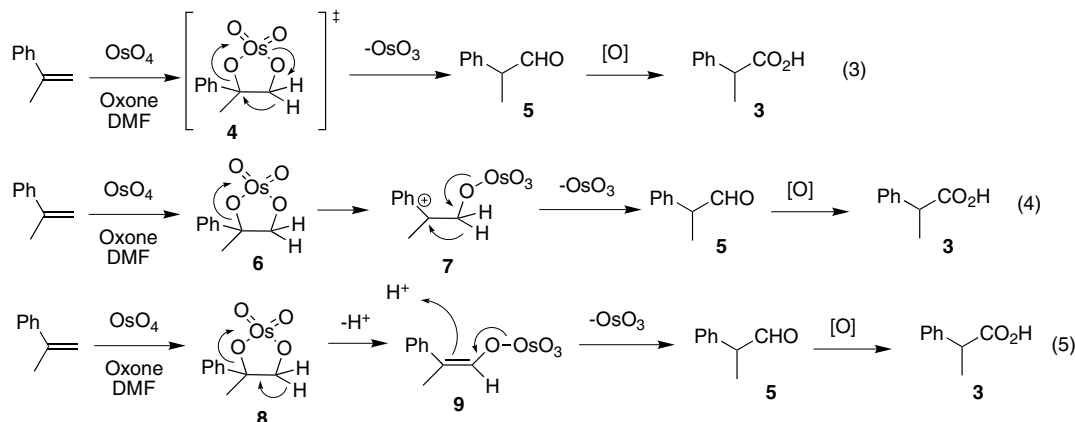
side product. The initial product from the fragmentation of the osmate ester is most likely the 2-phenylpropionaldehyde (**5**). This substance (not observed by ^1H NMR or GC of the product mixtures) would be readily oxidized to the observed carboxylic acid **3** by action of Oxone.¹² Scheme 2 shows three possible routes to 2-phenylpropionaldehyde (**5**). Eq. 3 invokes a 1,2-hydride shift from the osmate ester intermediate (transition state **4**) that would lead to the aldehyde by way of a concerted process. One can also imagine the formation of the aldehyde intermediate **5** by two two-step pathways. Eq. 4 suggests the intermediacy of carbocation **7** resulting from initial dissociation of osmate ester **6** followed by hydride shift. Eq. 5 suggests the intermediacy of enolate species **9** resulting from the deprotonation of the initial osmate ester intermediate **8**. While at this point, none of these possibilities can be ignored, one can speculate on the merits of each case. Eqs. 3 and 4 are similar in that they both rely on a 1,2-hydride transfer. It is not clear at this point, whether the formation of the stable tertiary benzylic carbocation **7** is necessary to allow for a 1,2-hydride shift. One might expect that if the hydride shift readily occurs without carbocation formation, then the problem of forming undesired products would be more systemic. The deprotonation/reprotonation sequence described in Eq. 5 also cannot be ruled out at this point, although the presence of enolate **9** under the relatively acidic reaction conditions seems suspect. We are currently investigating the origin of 2-phenylpropanoic acid (**3**) in this particular reaction, and the results of this study will be presented in due course.

Table 2. Observed side products from the cleavage of α -methylstyrene^a

Osmium source			
	1	2	3
OsCl_3	90%	3%	7%
$\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$	95%	2%	3%
P.B. OsO_4	82%	2%	16%
OsEnCat	71%	3%	26%
OsO_4	84%	3%	12%

^a GC yields.

Finally, we also evaluated the ability to recycle the encapsulated osmium tetroxide, OsEnCatTM when employed as the catalyst in our methodology. When 0.02 equiv of OsEnCatTM was employed in successive cleavage runs with *trans*-stilbene (Table 3), the catalyst was readily recycled, allowing for the same sample of OsEnCatTM to be employed in up to three sequential reactions. The immobilized catalyst was easily recovered by vacuum filtration, followed by washing with water and ethyl acetate to remove residual salts and cleavage product. While the catalyst proved non-recyclable at lower catalyst loadings, it is noteworthy that OsEnCatTM performs amiably at a remarkably low 0.0025 equiv



Scheme 2. Possible mechanisms for the formation of 2-phenylpropionic acid.

Table 3. OsEnCat™ recyclability study^a

Run	OsEnCat™ (equiv)	Yield (%)
1	0.02	73
2	0.02	85
3	0.02	56
4	0.02	Inc.

Note: Inc. = reaction did not proceed to completion after 12 h. Yields are isolated yields.

^a After each run, OsEnCat™ was recovered and reused in the subsequent run without modification.

catalyst loading in the oxidative cleavage of activated substrates (e.g., *trans*-stilbene (Table 1, entry 1)).

In summary, the osmium-mediated oxidative cleavage of olefins is compatible with various different osmium sources. The ability to employ less volatile and more innocuous osmium sources without sacrificing yield or purity of the desired product should serve to enhance the usefulness of this mild and effective method for the oxidative cleavage of olefins.

Acknowledgement

The authors thank Professor Ley for kindly providing a sample of OsEnCat™ for this study.

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- General procedure for the oxidative cleavage of olefins: The osmium source and Oxone (4 equiv relative to olefin) were added to DMF (0.2 M based on olefin) at RT. Osmium loadings varied as follows: 0.01 equiv was employed when osmium tetroxide, osmium trichloride, or potassium osmate was employed. Polymer-bound osmium tetroxide was used in either 0.001 equiv or 0.01 equiv depending on the substrate as indicated in Table 1. OsEnCat™ was employed in either 0.0025 equiv or 0.01 equiv depending on the substrate as indicated in Table 1. When osmium trichloride or potassium osmate were employed, the resulting mixture was stirred for 0.5 h to allow for pre-oxidation of the catalyst, after which time the olefin (1 equiv) was added in one portion and the resultant mixture was rotated for 12 h. For all other osmium sources, the olefin was added directly after the addition of the osmium source and Oxone. After the reaction was judged to be complete by TLC, the resulting mixture was poured into a separatory funnel and the remaining Os(VIII) was reduced by adding an equal volume of a saturated sodium sulfite solution. The resulting slurry was then extracted with ethyl acetate (3×). The combined organics were then washed with 1 N HCl (3×) and brine, dried over Na₂SO₄, and concentrated by rotary evaporation. The crude products were purified by silica gel chromatography or recrystallization where necessary. *Caution:* We have noted that these reactions can become quite exothermic, especially when conducted on a large scale. For larger scale reactions (greater than 2 mmol of olefin), we recommend cooling the solution of osmium source and Oxone on an ice bath before the addition of olefin and allowing the reaction mixture to warm slowly to room temperature.
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