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Catalytic oxidative cleavage of olefins promoted by osmium tetroxide and hydrogen peroxide

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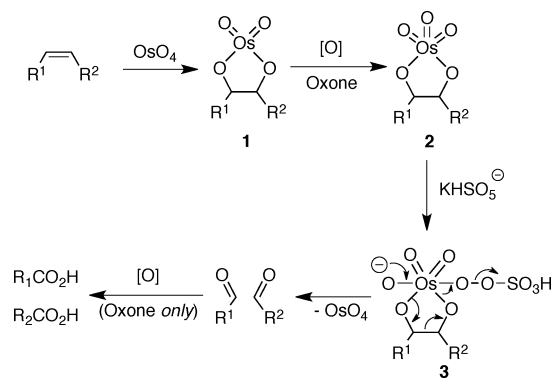
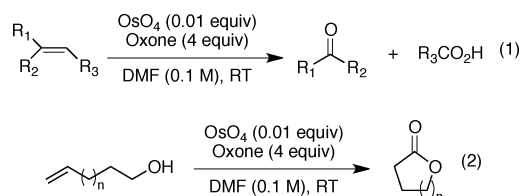
Hydrogen peroxide was employed as the terminal oxidant in the osmium tetroxide mediated oxidative cleavage of olefins, producing the corresponding aldehyde and ketone products. Aryl olefins are cleaved in good to excellent yield regardless of arene electronics. Alkyl olefins cleave in moderate to good yield for di- and tri-substituted alkenes.

Oxidative cleavage of olefins is one of the most prevalent reactions in organic synthesis. The two main oxidative cleavage pathways can be summarized as conversion of olefins to vicinal diols and subsequent cleavage with NaIO_4 or other oxidants¹ and ozonolysis in which the olefin is directly cleaved into functionalized products depending on workup conditions.² Ozonolysis is quite reliable, but has always had major safety concerns. Ozone gas is highly toxic and its generation requires specialized equipment.³ Examples of alternate reactions to ozonolysis include Noyori's⁴ cleavage of olefins to carboxylic acids with hydrogen peroxide and Na_2WO_4 , Ranu's⁵ $\text{InCl}_3/t\text{-BuOOH}$ cleavage of alkenes and alkynes to carboxylic acids, and several other transition metal mediated protocols.⁶ In this manuscript, we report an oxidative cleavage of aryl and alkyl olefins to the corresponding aldehydes, catalyzed by OsO_4 , employing H_2O_2 as the terminal oxidant.

Previously, we reported an osmium based catalytic oxidative cleavage of olefins without the intermediacy of diols (Scheme 1).^{7,8} The initial report used a catalytic portion of osmium tetroxide with several equivalents of Oxone (a triple salt containing two parts KHSO_5 , one part KHSO_4 , and one part K_2SO_4), which facilitated the cleavage of a variety of olefins to the corresponding carboxylic acids (for mono- and vicinal disubstituted alkenes) or ketone (for geminal disubstituted alkenes). Trisubstituted olefins yielded the corresponding carboxylic acids and ketones with only a minimal

modification to the general procedure. Esters and lactones were accessible if alcohols were used as solvent or an alcohol was present in the alkenyl molecule.⁹ The reaction's utility was highlighted in the efficient total synthesis of (+)-tanikolide.¹⁰

Scheme 2 illustrates the postulated mechanism for the oxidative cleavage of olefins with OsO_4 and Oxone. After an initial $[3 + 2]$ osmylation event, the resultant osmium(VI) glycolate **1** is proposed to undergo further oxidation to the osmium(VIII) glycolate **2**. Upon nucleophilic attack from the external oxidant (*i.e.* KHSO_5), fragmental collapse of **3** effects the glycolate cleavage, generating the aldehyde cleavage products. The aldehydic products are further oxidized with Oxone to the corresponding carboxylic acids *via* a Baeyer–Villiger type pathway. Earlier, we found that use of soluble Oxone ($\text{nBu}_4\text{NHSO}_5$) attenuated the reactivity of the system such that the aldehyde products could be generated without further oxidation.¹¹

Scheme 2 Proposed OsO_4 -mediated cleavage mechanism with Oxone.Scheme 1 Oxidative cleavages mediated by OsO_4 /Oxone.

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Herein we attempted to induce a similar oxidative cleavage with the greener H_2O_2 (H_2O as byproduct) as the terminal oxidant in order to address the considerable salt stream associated with the Oxone and $\text{nBu}_4\text{NHSO}_5$ protocols. Indeed, the overall process depicted in Scheme 2 requires 4 molar equivalents of the active oxidant, KHSO_5 , per equivalent of olefin substrate. Based on the composition of commercial Oxone, the requisite two equivalents of that reagent generate a remarkable 8 molar equivalents of salt waste per mole of substrate! The successful replacement of Oxone with hydrogen peroxide would significantly reduce the waste associated with the transformation.

Table 1 Oxidative cleavage of styrene and methyl cinnamate in various solvents

Entry	Solvent	Styrene		Methyl cinnamate	
		4:5	%yield	4:5	%yield
1	Benzene	6.3 : 1	53	6.9 : 1	86
2	DMF	3.8 : 1	71	8.0 : 1	77
3	CH ₃ CN	3.9 : 1	63	23.2 : 1	99
4	MeOH	6.3 : 1	54	7.1 : 1	94
5	EtOH	6.4 : 1	48	8.6 : 1	82
6	Et ₂ O	5.1 : 1	52	4.8 : 1	31
7	DCM	4.8 : 1	33	6.3 : 1	97
8	CHCl ₃	4.4 : 1	29	8.3 : 1	82

All reactions carried out in the presence of 0.05 mmol of dodecane (ISTD). Yields are based on GC analysis utilizing an internal standard normalized with a calibration curve.

As a starting point, we initially investigated a direct analogue of our previously developed reaction conditions (see Scheme 1, eq. 1) whereby we replaced Oxone with a 50% aqueous hydrogen peroxide solution. These initial experiments gave unsatisfactory results for several aryl olefins. Subsequently, DMF was replaced with a variety of solvents (CH₃CN, benzene, THF, MeOH, EtOH, Et₂O, cyclohexane, hexane, CHCl₃, and DCM). Initially, it was found that addition of some amount of DMF to various solvents facilitated the desired oxidative cleavage, thus 20 equiv of DMF was used as a standard additive. The test olefins were stilbene, styrene, and methyl cinnamate. Happily, stilbene cleaved well in most solvents (~100% conversion) except for cyclohexane and hexane, which showed significant amounts of starting material after 24 h. The data for styrene and methyl cinnamate in various solvents are tabulated in Table 1. For methyl cinnamate, CH₃CN was clearly superior, producing primarily the desired benzaldehyde **4** in 99% yield. For electron neutral olefins (like styrene) CH₃CN works well, though it does not provide the best yield. In order to have a consistent methodology, CH₃CN was chosen as the standard solvent for further studies.^{12–14}

As indicated in Table 1, the product of the oxidative cleavage mediated by hydrogen peroxide was benzaldehyde, with only a minimal amount of benzoic acid being detected in most cases (<15%). This differs from the Oxone-mediated reaction, which yielded only carboxylic acids. This is presumably due to the relative inability of H₂O₂ to engage in Baeyer–Villiger chemistry with the product aldehydes.

Next, several aryl olefinic substrates were screened to assess the substrate scope of the transformation (Table 2). The necessity of including DMF was probed by performing parallel reactions with 0 and 20 equiv of DMF. Interestingly, the addition of DMF was warranted in some cases, but detrimental in others. While the cleavage of styrene (entry 1) was unaffected by the presence of DMF (48% vs. 46% yield), the inclusion of DMF in the cleavage of stilbene (entry 2) led to a significant drop in yield (93% to 77%). Electron-poor substrates, however, benefit from the addition of DMF. Methyl cinnamate (entry 3), cinnamic acid (entry 4), and 2-methyl-cinnamic acid (entry 5) were cleaved efficiently in the presence of DMF, generating benzaldehyde in yields ranging from

Table 2 Substrate scope for OsO₄/H₂O₂ cleavage of aryl olefins

Entry	R ¹	R ²	20 equiv DMF	0 equiv DMF
			% 4 (5)	% 4 (5)
1	H	H	48 (4)	46 (5)
2	Ph	H	77 (0)	93 (7) ^a
3	CO ₂ Me	H	71 (4)	23 (0)
4	CO ₂ H	H	76 (24)	45 (8)
5	CO ₂ H	Me	66 (9)	51 (15)
6	CHO	H	29 (6)	15 (15)
7	CH ₂ OAc	H	61 (8)	68 (8)
8	CH ₂ OH	H	50 (8)	67 (5)
9	α-Methylstyrene	—	78 ^b	86 ^b
10	Dibenzoylethylene	—	0 (93) ^a	0 (94) ^a
11	α-Vinylbenzyl alcohol	—	65 (4)	54 (11)

All reactions carried out in the presence of 0.05 mmol of tetraglyme (ISTD). Yields are based on GC analysis utilizing an internal standard normalized with a calibration curve.^a Yields account for the generation of 2 equiv of **4** or **5**. ^b Yield of acetophenone.

66–71%. This stands in contrast to the yields when DMF was not employed (23–51%, entries 3–5). The yields for the cleavage of cinnamaldehyde were generally lower than the other electron poor olefins, but the preference for the presence of DMF is still apparent (29% w vs. 15%, entry 6).

Cinnamyl alcohol acetate (entry 7) and cinnamyl alcohol (entry 8) showed a slight preference for the exclusion of DMF, but the effect was less pronounced than for the more strongly electron poor olefins. The cleavage of α-methylstyrene (entry 9) showed that the reagent combination is also able to cleave geminally disubstituted olefins, producing acetophenone in 78 and 86% yield with and without the DMF additive, respectively. In cases where the initial cleavage protocol returns α-keto (entry 10) or α-hydroxy (entry 11) aldehydes, the initial cleavage products rapidly underwent Baeyer–Villiger rearrangement and hydrolysis to produce the observed benzoic acid and benzaldehyde products, respectively, similar to our previous observations with KHSO₅.¹⁵

We next sought to evaluate the course of the reaction when alkyl substituted olefins were employed as substrates. Initial experiments employing our standard conditions in the cleavage of 1-decene produced a complex mixture of oxidized products (Scheme 3). While vicinal diol **6** was the major product (>45% yield), we also observed the production of more highly oxidized products including α-hydroxy ketone **7** (30–40% yield), as well as the desired cleavage products (aldehyde **8** and carboxylic acid **9**) in lower yields (~15% of the mixture). Additionally, we detected trace amounts of the appropriate epoxide. We never observed the formation of the potentially viable α-hydroxyaldehyde product.

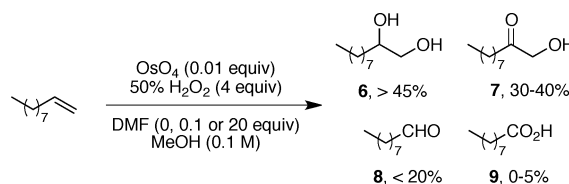
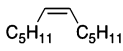





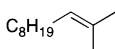

**Scheme 3** OsO₄/H₂O₂ cleavage of 1-decene.

Table 3 OsO₄/H₂O₂ cleavage of alkyl olefins

$ \begin{array}{c} \text{R}^1 \text{---} \text{C} = \text{C} \text{---} \text{R}^3 \\ \\ \text{R}^2 \end{array} $ $ \xrightarrow[\text{DMF (X equiv)}]{\text{OsO}_4 (0.01 \text{ equiv})} $ $ \xrightarrow[\text{CH}_3\text{CN (0.1 M), rt}]{50\% \text{ aq. H}_2\text{O}_2 (4 \text{ equiv})} $ $ \text{R}^1\text{CHO} + \text{R}^1\text{CO}_2\text{H} $ $ \text{R}^2, \text{R}^3 = \text{Alkyl or H} $				
		0 equiv DMF	0.1 equiv DMF	20 equiv DMF
Substrate	Product	% 10 (11)	% 10 (11)	% 10 (11)
		34 (0) ^a	33 (0) ^a	38 (0) ^a
		39 (5) ^a	42 (3) ^a	52 (3) ^a
		65	75	90
		66 (2)	72 (3)	64 (1)

All reactions carried out in the presence of 0.05 mmol of tetraglyme (ISTD). Yields are based on GC analysis utilizing an internal standard normalized with a calibration curve.^a Yields account for the generation of 2 equiv of hexanal or pentanal.

Unfortunately, significant efforts to tune the reaction conditions to favor formation of cleavage products were unproductive. We investigated the addition of varying equivalents of DMF (0, 0.1, and 20 equiv), multiple solvents (with methanol providing the highest yields of the desired aldehyde), and acidic and basic additives, but these efforts failed to improve upon the results depicted in Scheme 3.

Although the OsO₄/H₂O₂ oxidative cleavage protocol proved difficult for 1-substituted monoalkylated olefins, more highly substituted alkyl olefins provided better results. When *cis*-6-dodecene (*cis* disubstituted), *trans*-5-decene (*trans* disubstituted), 2-butyl-1-hexene (geminal disubstituted), and 2-methyl-2-undecene (trisubstituted) were treated under our standard reaction conditions, the desired cleavage products were generated in acceptable yields ranging from 33–90% (Table 3). Importantly, the generation of diol products was minimal. Additionally, the formation of the carboxylic acid cleavage product was typically below 5%. While the cleavage of the 1,2-*cis* example was relatively unaffected by the presence or absence of DMF (33–38%), the 1,2-*trans* example benefited from the presence of the additive. In the latter case, the yield of pentanal steadily increased from 39% with no DMF to 52% with 20 equiv. Similarly, the geminally disubstituted example was cleaved to 5-nonanone with yields increasing up to 89% in the presence of 20 equiv of DMF. The tri-substituted example, 2-methyl-2-undecene, was also readily cleaved to nonanal in yields ranging from 64–72%, with a slight preference for the presence of 10 mol% DMF in the reaction mixture. While the formation of diol and carboxylic acid byproducts were nearly completely suppressed with the alkyl olefins, the major by-products for the *cis*- and *trans*-disubstituted olefins as well as the tri-substituted olefin were the α -hydroxy-ketone (20–30%). In a demonstration of scalability, oxidative cleavage of stilbene (1.0 g, 5.5 mmol) in CH₃CN was performed, yielding benzaldehyde in 87% purified yield.¹⁶

It warrants emphasis that the unique DMF effects observed in Tables 2 and 3 indicate an important means for tuning and

optimizing the reactivity of the OsO₄/H₂O₂ system for a particular substrate. In some cases the inclusion or exclusion of the DMF additive can greatly influence the overall yield of the desired cleavage products. At this time, the exact role of this additive is not clear.

In a final series of experiments we also evaluated the course of the reaction with alkyl substituted olefins when alternate sources of hydrogen peroxide were employed. The series of alkyl substituted olefins were screened in the presence of ethereal hydrogen peroxide under anhydrous conditions in dry methanol. We screened the series with varying degrees of added moisture (0, 14, and 28 equiv of H₂O). In general this particular protocol was less useful, returning the desired cleavage products in lower yields than those depicted in Table 3 (yields ranging from 18–51%). Similarly, urea peroxide was also ineffective, returning the desired cleavage products in yields ranging from 10–55%. In these cases the major products were the undesired α -hydroxyketones.

In conclusion, we have succeeded in effecting the oxidative cleavage of olefins mediated by osmium tetroxide by modifying our existing protocol to allow for the use of the more environmentally benign hydrogen peroxide as the terminal oxidant in lieu of Oxone. The successful implementation of this plan has allowed us to address concerns about the substantial salt stream associated with our original protocol. In doing so, we have developed a useful protocol for the oxidative cleavage of aryl and alkyl substituted olefins, granting access to aldehyde or ketone oxidative cleavage products in moderate to excellent yields. We have noted an interesting DMF additive effect that may provide a useful means for tuning and optimizing the yield of the cleavage reaction for particular substrates.

Acknowledgements

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- 12 An Agilent Technologies 6850 Series II Network GC System equipped with an Agilent Tech. 6850 Series II Auto Sampler was used for analysis. The column used for all experiments was an Agilent Tech. J&W Scientific High Resolution Gas Chromatography Column (19091Z-413E HP-1) with the following specifications: Length (m) 30, I.D.(mm) = 0.32, Film (μL) = 0.25, and temperature limits = -60° to 325°C (350°C). Method: Injection Temp. = 250°C , Ramp = 60°C , Make-up gas = Helium, Mode = Constant Pressure, Detector Temp. = 250°C , Ramp = 60°C for 2 min. then ramped at $10^\circ\text{C min}^{-1}$. until 300°C then hold for 5 min.
- 13 General Procedure for standard curves. A stock solution of the substrates and ISTD were made. Varying amounts of substrate (0.01, 0.02, 0.03, ... mmol) and a constant amount of ISTD (0.05 mmol) were combined and then the total volume taken to 1 ml. The solutions were injected in the GC and the peak area ratio was determined ([Substrate]/[ISTD]). These were plotted to produce a straight line.
- 14 General Procedure for oxidative cleavage. Stock solutions of substrate and internal standard (ISTD) [tetraglyme or dodacene] were made. Next, 0.1 mmol of substrate was aliquoted into a 3.5 mL vial followed by 0.5 mmol of ISTD (substrate to ISTD ratio was 2:1). The vials were diluted to 1 mL of solvent, including additives (DMF) 0.01 eq. (5 μL) of OsO_4 (1 g/20 mL toluene solution) was added and stirred for five minutes. Finally, 4 equiv (50 μL) of 50% hydrogen peroxide in water was added. The solutions were stirred over night after which they were injected into the GC. The chromatograms were compared with a standard curve for analysis.
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- 16 Procedure for large-scale oxidative cleavage. Stilbene (5.5 mmol, 1 g) was dissolved in CH_3CN (55 mL, 1 M). OsO_4 (0.01 equiv, 28 μL , 1 g/20 mL toluene solution) was added and stirred for five minutes. Hydrogen Peroxide (7.3 equiv, 376 mL of a 50% solution) was added and stirred for 4 h. The reaction was quenched with a saturated sodium sulfite solution and then extracted (3X) with EtOAc. The combined organics were washed with water (3X) to yield the crude product as an oil. Column chromatography purification of the crude with 20% EtOAc and hexanes yielded benzaldehyde in 87% yield.