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Oxidative Cleavage of Alkenes Using an In Situ Generated Iodonium Ion with Oxone as a Terminal Oxidant

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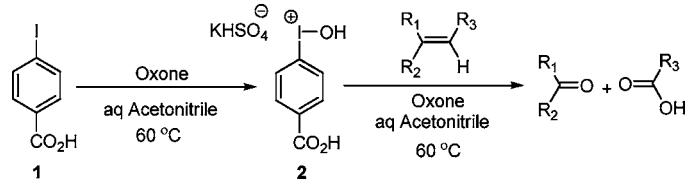
ABSTRACT



A facile and operationally convenient catalytic procedure for oxidative cleavage of alkenes is described. In situ formed [hydroxy-(4-carboxyphenyl)iodonium]ion, 2, from the oxidation of 4-iodobenzoic acid, 1, has been shown to facilitate the cleavage of a variety of alkenes in presence of Oxone as a co-oxidant. Optimization of the reaction conditions using 1-phenyl-1-cyclohexene, 3, and the competitive oxidative cleavage of different substrates using the optimized conditions has uncovered important mechanistic details of the reaction.

The oxidative functionalization and cleavage of alkenes represents a broad class of fundamental transformations in organic chemistry frequently employed both in academic and industrial settings for the synthesis and production of valuable intermediates and chemical commodities.[1] Scission of olefins to aldehydes, ketones, and carboxylic acids is often carried out using ozonolyis, accompanied by the appropriate workup.[1c,d,2] Alternatively, alkenes can also be cleaved using the Lemieux-Johnson Protocol (OsO_4 followed by $NaIO_4$).[3] OsO_4 is also the choice reagent for the *syn*-hydroxylation of olefins.[1c,d,4] The utility of these popular methods for oxidative transformation of alkenes is often hampered by the safety concerns of ozonolysis[5] and the toxicity of OsO_4. During the last few decades several attempts have been made by different groups to devise safer alternatives for these useful reactions. Prominent among these are the use of high-valent metal-oxo catalysts, including complexes bearing Mn,[6] Mo,[7] Ru,[8] Pd,[9] Re,[10] and Os.[11] In these cases, a co-oxidant is employed to regenerate the active catalyst.

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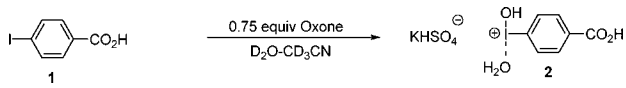
Despite the popularity of these transition metal catalyzed reactions, the toxicity associated with these metals and the inability to recover 100% of the spent reagent raises concerns and obstructs their use in industrial processes. Attempts have been made to recover osmium catalysts after oxidation by immobilization[12] or microencapsulation[13] of the catalysts on polymers. In keeping with green trends in organic synthesis, Ochiai et al. introduced environmentally benign organoiodine reagents[14] [PhIO, 48%HBF_4, 18-Crown-6[14a] and ArI (cat), 48% HBF_4, *m*CPBA[14b]] for the oxidative cleavage of alkenes. More recently, Nicolaou reported a one-pot combination of hydroxylation (Upjohn conditions[15]) followed by the addition of stoichiometric $Ph(IOAc)_2$ to effect alkene cleavage.[16] Continuing our interest in developing catalytic and selective oxidation protocols using water-soluble hypervalent iodine reagents in presence of Oxone as a co-oxidant,[17] we reasoned that the oxidation of 4-iodobenzoic acid (4-IBAcid, **1**) with Oxone would yield [hydroxy(4-carboxyphenyl)-iodonium]ion, **2**, a structural derivative of the active reagent reported by Ochiai et al. for alkene functionalization (Scheme 1).[14a] Herein, we report a facile

Scheme 1. Oxidation of 4-IBAcid by Oxone

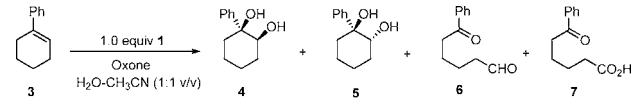


and operationally convenient protocol for the oxidative cleavage of alkenes and vicinal diols in aqueous acetonitrile using catalytic amounts of 4-IBAcid in the presence of Oxone as a terminal oxidant.

Our initial efforts were directed at establishing the easy oxidation of **1** with Oxone in aqueous acetonitrile to produce the corresponding iodonium ion, **2,** the desired active reagent. Treatment of **1** with 0.75 equiv of Oxone in D_2O/CD_3CN (3:1 v/v) readily provided **2**. However, we also noted that the oxidation of **1** carried out in 2:1 and 1:1 v/v D_2O and CD_3CN were incomplete as evident from the presence of the deshielded AA′BB′ signals due to **2** along with the upfield signals of **1** in the corresponding ^1H NMR spectra. The apparent difference in the extent of oxidation in the three solvent mixtures may be a reflection of the solubility differences of **1** and **2** in the respective media. [Hydroxy(phenyl)iodonium] ion (obtained by protonation of iodosyl benzene) is known to be readily soluble in H_2O at pH <2.3.[18] Thus, it is not surprising that in the acidic oxidation medium, **2** is more soluble in solvent mixtures with higher concentration of D_2O. Having established that **2** can readily be formed from the oxidation of **1** we set out to investigate the utility of **2** as an in situ generated reagent for oxidative cleavage of alkenes. Commerically available 1-phenyl-1- cyclohexene **3** was chosen as the test substrate upon which optimization studies were performed.

In this study, we chose to focus our initial attention on determining whether Oxone alone promoted alkene cleavage. Entries 1 and 2 of Table 1 demonstrate that while Oxone

Table 1. Optimization Studies with 1-Phenyl-1-Cyclohexene, **3**[a]



	equiv		% yield[b]		
entry	**1**	oxone	(**4** + **5**)	**6**	**7**
1	–	0.5[c]	95	–	–
2	–	1.0[c]	100	–	–
3	1.0	0.5	95	5	–
4	1.0	0.75	69	7	24
5	1.0	1.0	45	15	40
6	1.0	1.2	25	10	65
7	1.0	1.5	8[d]	–	92
8	1.0	1.63	3[d]	5	92
9	1.0	2.0	–	–	100
10	0.5	2.0	–	–	100
11	0.25	2.0	–	–	100
12	0.05	2.0	–	–	100

[a] Reactions were carried out on 0.2 g scale in H_2O:CH_3CN (1:1 v/v, 20 mL) at 60 °C for 3 h. [b] ^1H NMR yield. [c] No 4-IBAcid present. [d] Exclusively **5** with no **4** present.

does convert alkene **3** to the diol products[19] **4** and **5**, no oxidative cleavage is observed. However, in the presence of 4-IBAcid, alkene **3** is cleaved to the corresponding oxidized products **6** and **7**. The yield of keto-aldehyde **6** and keto-acid **7** is dependent on the ratio of 4-IBAcid to Oxone. Entries 3−9 demonstrate that in the presence of 1.0 equiv of **1**, varying equivalents of Oxone results in changes in product distribution; an increase in Oxone concentration is met with a parallel increase in formation of cleaved products **6** and **7**. The yield of **6** is never high due to rapid aldehyde oxidation to **7** by Oxone.[20] We identified that 1.5−2.0 equiv of Oxone proved sufficient for complete conversion of **3** (a trisubstituted alkene) to **7** (a keto-acid).[21] The isolated product mixture from this optimization study contained small (<20%) amounts of **1** (see Supporting Information) indicating

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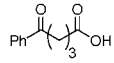
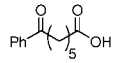
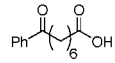
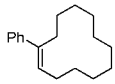
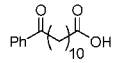
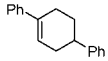
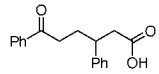
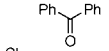
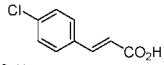
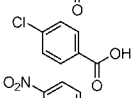
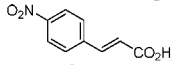
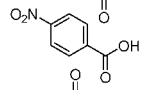
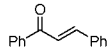
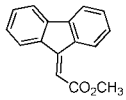
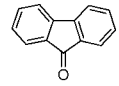
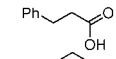
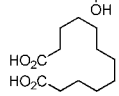
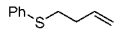
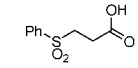
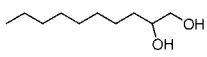
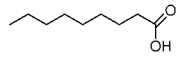
that the major bulk of the stoichiometric amount of **1** initially employed in these reaction was lost during the workup either as the water-soluble iodonium ion, **2**, or through the polymerization of the iodosyl derivative. Irrespective of how the loss of **1** occurred, the observed quantitative cleavage of **3** with only substoichiometric amounts of **1** indicated the feasibility of a catalytic protocol which we verified by using substoichiometric quantities of **1** along with 2.0 equiv of Oxone to obtain near quantitative cleavage of **3** (entries 10−12).

These optimization studies with stoichiometric **1** served as a proof of principle that our in situ generated oxidant **2** effectively cleaves alkenes in the presence of Oxone. The ability to use **1** catalytically, in concert with the operational simplicity of this reaction, prompted us to investigate the scope of this transformation. Table 2 shows a selection of alkenes cleaved under the newly developed conditions. It should be noted that in the course of our studies we found that chromatographic separation of 4-IBAcid from desired products was occasionally difficult. To circumvent this problem, we found that iodobenzene can also be employed as a precatalyst without noticeable detriment to reaction performance. Left over iodobenzene after the reaction can then be easily removed under vacuum, simplifying product purification.

Table 2. Substrate Scope of Alkene Oxidative Cleavage

entry	substrate	method[a]	time h	product	yield, %
1		A	3		90[b]
2		A	3		76[b]
3		B	4		78[b]
4		A	3		80[b]
5		B	3		65[b]
6		A	6		83[c]
7		A	14		81[c]
8		A	14		90[c]
9		A	18		87[c]
10		A	14		33[c]
11		C	8		90[b]
12		C	8		82[c]
13		C	8		70[b]
14		C	8		86[c]

[a] Method A: 0.2 equiv of 1 and Oxone in H_2O-CH_3CN (1:1, v/v). Method B: 0.2 equiv of iodobenzene and Oxone in H_2O-CH_3CN (1:1, v/v). Method C: 1.0 equiv of Iodobenzene and Oxone in H_2O-CH_3CN (1:1, v/v). [b] Isolated yield. [c] ^1H NMR yield.

Phenyl conjugated cyclic alkenes are smoothly cleaved to the corresponding keto-acids. Electron deficient alkenes required prolonged reaction times (entries 7−10) for cleavage. To highlight the utility of the reaction it should also be noted that cleavage of **3** and other phenyl conjuagted cycloalkenes (entries 1−5) were carried out on multigram sccale (2−5 g) with no loss in yield. Cleavage of *trans*-chalcone gave only benzoic acid as the product as initially formed phenylglyoxalic acid is presumably further oxidized by Oxone to benzoic acid.[22] While 1-phenyl cyclododecene (entry 4) was easily oxidized, its des-phenyl counterpart (entry 12) suffered from slow oxidative cleavage. In general, we found that the rate of cleavage of phenyl conjugated cyclic alkenes were considerably faster than phenyl conjugated acylic alkenes.

Nonphenyl conjugated alkenes cleaved the slowest often requiring 24−36 h for completion. We also observed that use of stoichiometric iodobenzene along with the required amount of Oxone[21] facilitated quantitative cleavage of these reluctant alkenes in 6−8 h (entries 11−13). It was also intresting to observe that oxidative transformation of the alkenyl sufide (entry 13) to 4-(p-toluylsulfonyl)butyric acid can be readily accomplished using two additional equiv of Oxone in the reaction (Method C) for the oxidation of the sulfur atom.[23]

We viewed our ability to use vicinal diols as substrates (entry 14) as an opportunity to gain further insight into plausible reaction mechanisms. Our earlier optimization studies had hinted that vicinal diols were intermediates en route to full oxidized products (Table 1). In order to rationalize further some of the trends we observed so far (e.g., relative difficulty in cleaving unconjugated alkenes, the role of vicinal diols along the reaction pathway, and the easier and faster cleavage of *cis*-diols over *trans*-diols) we decided to perform a series of competition experiments to more clearly understand this newly developed reaction.

Competition experiments between **3** and **8** and between **4/5** and **11** were conducted under our catalytic conditions (20 mol % **1** and required amount of Oxone[21] in a 1:1 v/v solution of D_2O/CD_3CN) and the relative ease of oxidation of competing substrates were monitored by the appearance of discernible ^1H NMR peaks from the products from the two substrates (see Supporting Information). Monitoring these competitive reactions clearly showed that **3** was cleaved significantly faster than **8** and the rate of cleavage of both **4** and **5** were faster than that of **11,** evidently indicating the

(21) Oxone required for quantitative cleavage of susbtrates depend on the nature of the substrates employed and whether the initially formed cleaved products are further oxidized.

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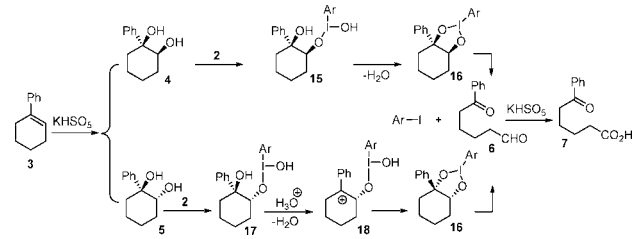
(24) Full competition experiment data is provided in the Supporting Information.

favorable effect of having a phenyl group on the bond being cleaved. We take it that the stability afforded by the phenyl ring on any build up of positive charge is responsible for observed rate differences (vide infra). More revealing data came from our studies of the cleavage of vicinal diols. During optimization studies we had observed that the *cis* diol **4** was cleaved faster than *trans* diol **5** and were curious whether such an observation offered us insight into a possible reaction mechanism. Head-to-head competition experiments between **11** and **12** clearly demonstrated that *cis*-1,2-cyclohexanediol, **11**, was cleaved faster than its *trans* counterpart, **12**. In comparing rates of cleavage of a mixture of **4**/**5** and **11** we noted that even *trans* alcohol **5** cleaved faster than **11**, underscoring the importance of presumably stabilizing an incipient carbocation. Additionally, competition experiments between **4**/**5** and **13** showed that **4** (and **5**) cleaved faster than **13**, suggesting that conformationally rigid *cis* diols are better substrates than open chain vicinal diols. No discernible rate differences in the cleavage of **11** and **13** were noted. This latter observation suggests that the conformational rigidity of the cyclic *cis* diols offsets the favorable role of a phenyl group on the bond cleaved in acylic substrates. Unconjugated acylic alkenes (**10**) and 1,2-alkanediols (**14**) cleaved only slowly, often requiring 24−36 h for completion under the catlaytic conditions (20 mol % **1** with requisite Oxone) tried. Cleavage of these sluggish substrates were, however, observed to be complete within 6−8 h when stoichiometric **1** or iodobenzene was employed. We believe that the slow rate of cleavage in these cases not only stems from the lack of favorable structural features in the substrates (phenyl group on the bond cleaved or conformationally rigid *cis*-diols) but also from the decomposition of the active reagent, **2** over time. Appearance of a singlet at δ 8.12[25] with its intensity increasing with a corresponding decrease in the intensity of the signals from **2** in the ^{1}H NMR spectra recorded at various intervals during the competitive reactions suggest such a decomposition.

On the basis of these studies, the following tentative mechanism for the oxidative cleavage of alkenes is proposed, using the cleavage of **3** as an example. The salient features of the mechanism shown in Scheme 2 are the following. The rapidly formed 1,2 diols **4** and **5** intercept the iodonium ion **2** to form intermediates **15** and **17** respectively. Cyclic dialkoxy-λ3-iodane **16**, readily formed from **15,** cleaves to give **6**, regenerating **1** ready to re-enter the reaction under catalytic conditions with enough Oxone present. Further oxidation of **6**→**7** consumes an additional 0.5 equiv of

(25) Spiking the ^{1}H NMR sample with terephthalic acid increases the intensity of the singlet at δ 8.12; however, formation of terephthalic acid in the reaction medium is still being debated.

Scheme 2. Suggested Mechanism for Cleavage of Alkenes



Oxone.[20] The sterically demanding ring puckering that would occur if a *trans* fused dialkoxy-λ3-iodane were to form from **17** forces the conversion of **17**→**16** via the benzylic carbocation **18**. The role of the phenyl group in stabilizing the carbocation intermediate in **18** explains the ease of oxidation of **5** over **11**. The proposed mechanism clearly shows that 1.5 equiv of Oxone is required for the conversion of **3**→**7**. Experimentally it was noted that 1.5−2.0 equiv of Oxone is required for quantitative cleavage and conversion of **3**→**7** and we believe that this slight discrepancy stems from the decomposition or polymerization of the iodonium ion **2** during the reaction accounting for the excess consumption of Oxone as noted.

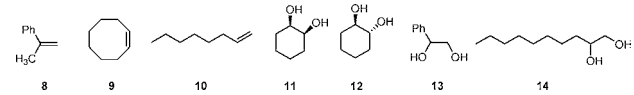


Figure 1. Substrates Used in Head-to-Head Competitive Oxidative Cleavage Reactions with **3** and **4**/**5**.[24]

In summary we have developed an operationally simple and catalytic procedure for oxidative cleavage of alkenes using benign and cheap reagents. The new method is versatile and a safer alternative to existing alkene cleavage procedures.

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Supporting Information Available: Experimental details and the spectral data of the isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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