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An Expedient Procedure for the Oxidative Cleavage of Olefinic Bonds with $PhI(OAc)_2$, NMO, and Catalytic OsO_4

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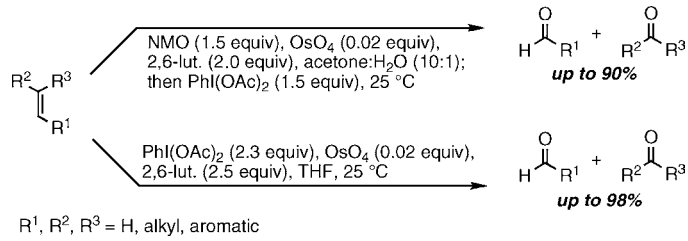
ABSTRACT



$PhI(OAc)_2$ in the presence of OsO_4 (cat.) and 2,6-lutidine cleaves olefinic bonds to yield the corresponding carbonyl compounds, albeit, in some cases, with α-hydroxy ketones as byproduct. A more practical and clean protocol to effect oxidative cleavage of olefinic bonds involves NMO, OsO_4 (cat.), 2,6-lutidine, and $PhI(OAc)_2$.

The oxidative cleavage of olefinic bonds, either through their ozonides or diols, is used widely in organic synthesis as a useful method to truncate carbon chains or, more usefully, to prepare carbonyl compounds. The most common methods employed to carry out these operations involve ozonolysis (Scheme 1a) or Johnson−Lemieux oxidation[1] [$NaIO_4$, OsO_4 (cat.)] and its variants[2] (Scheme 1b), including the recent improvement (addition of 2,6-lutidine) introduced by Jin et al.,[3] all of which are one-step procedures. The disadvantages involved with these methods (e.g., safety,[4] drastic or inconvenient conditions) led to the introduction of the two-step procedure employing sequential Upjohn dihydroxylation[5] [NMO, OsO_4 (cat.)] and periodate cleavage of the resulting 1,2-diol (Scheme 1c), which became as popular, if not more, than the first two methods. More recent attempts to improve upon these protocols led to the procedures of Borhan et al.[6] [oxone, OsO_4 (cat.)] and Ochiai et al.[7] [*m*-CPBA, HBF_4, ArI (cat.)] that oxidatively cleave olefinic bonds. The use of strong conditions, and the fact that both

(1) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478–479.

(2) (a) Okumoto, H.; Ohtsuko, K.; Banjoya, S. *Synlett* **2007**, 3201–3205. (b) Brooks, C. D.; Huang, L. C.; McCarron, M.; Johnstone, R. A. W. *Chem. Commun.* **1999**, 37–38. (c) Antonelli, E.; D'Aloisio, R.; Gambaro, M.; Fiorani, T.; Venturello, C. *J. Org. Chem.* **1998**, *63*, 7190–7206. (d) Sato, K.; Aoki, M.; Noyori, R. *Science* **1998**, *281*, 1646–1647. (e) Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4745. (f) Ishii, Y.; Yamawaki, K.; Ura, T.; Yamada, H.; Yoshida, T.; Ogawa, M. *J. Org. Chem.* **1988**, *53*, 3587–3593. (g) Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1978**, *43*, 1532–1536.

(3) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.

(4) (a) Dorofeev, S. B.; Eletskii, A. V.; Smirnov, B. M. *Dokl. Akad. Nauk SSSR* **1981**, *257*, 592−596. (b) Koike, K.; Inoue, G.; Fukuda, T. *J. Chem. Eng. Jpn.* **1999**, *32*, 295–299. (c) Ogle, R. A.; Schumacher, J. L. *Process Saf. Prog.* **1998**, *17*, 127–133.

(5) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973–1976.

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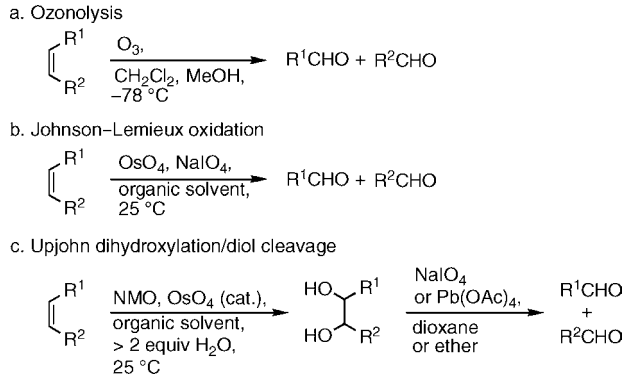
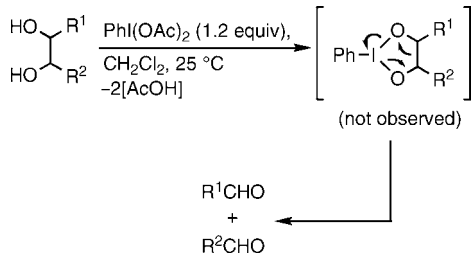
Scheme 1. Common Methods for Cleaving Olefinic Bonds to Carbonyl Compounds



Scheme 2. Cleavage of 1,2-Diols to Aldehydes by $PhI(OAc)_2$



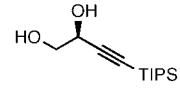
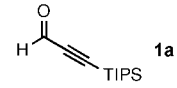
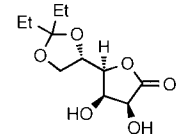
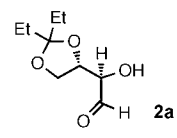
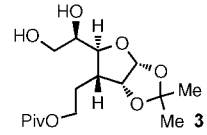
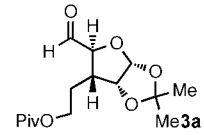
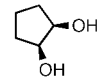
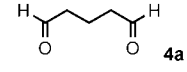
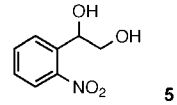
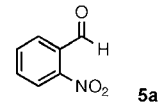
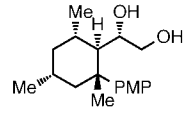
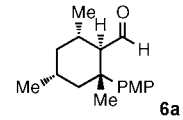
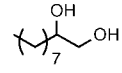
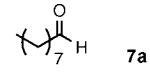
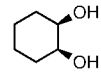
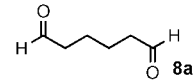
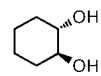
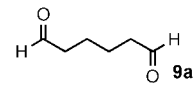
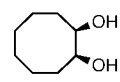
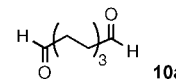
of these procedures lead to carboxylic acids, also endows them with certain limitations.

As part of a total synthesis program, we recently developed practical and convenient protocols for cleaving 1,2-diols and olefinic bonds to aldehydes and ketones employing hypervalent iodine reagents [e.g., $PhI(OAc)_2$][8] as the main oxidant (Scheme 2). In this paper, we highlight the practicality of using $PhI(OAc)_2$ to achieve a clean oxidative cleavage of 1,2-diols and demonstrate its compatibility and effectiveness in oxidatively cleaving olefinic bonds into the corresponding carbonyl compounds when coupled with dihydroxylation conditions.

$PhI(OAc)_2$ is an excellent reagent for the cleavage of 1,2-diols,[9] and it is rather surprising that it is not commonly employed in that capacity, despite a seven decade old publication by Criegee and Beucker[8] demonstrating its ability to effect this transformation. More recently, Arseniyadis et al. elegantly employed this reagent to initiate cascade sequences that lead to novel heterocyclic systems through transient dialdehydes.[9a] A polymer-supported version of this reagent has also been reported, but its use has been limited.[10]

The rarity of reports[11] using $PhI(OAc)_2$ to cleave 1,2-diols can be attributed to the absence of a systematic study demonstrating its capabilities in this regard. Thus, in order to illustrate the generality and scope of $PhI(OAc)_2$ as an efficient 1,2-diol cleaving reagent, and as a prelude to our subsequent investigations, we employed it to that effect on a variety of diol substrates as shown in Table 1 (entries

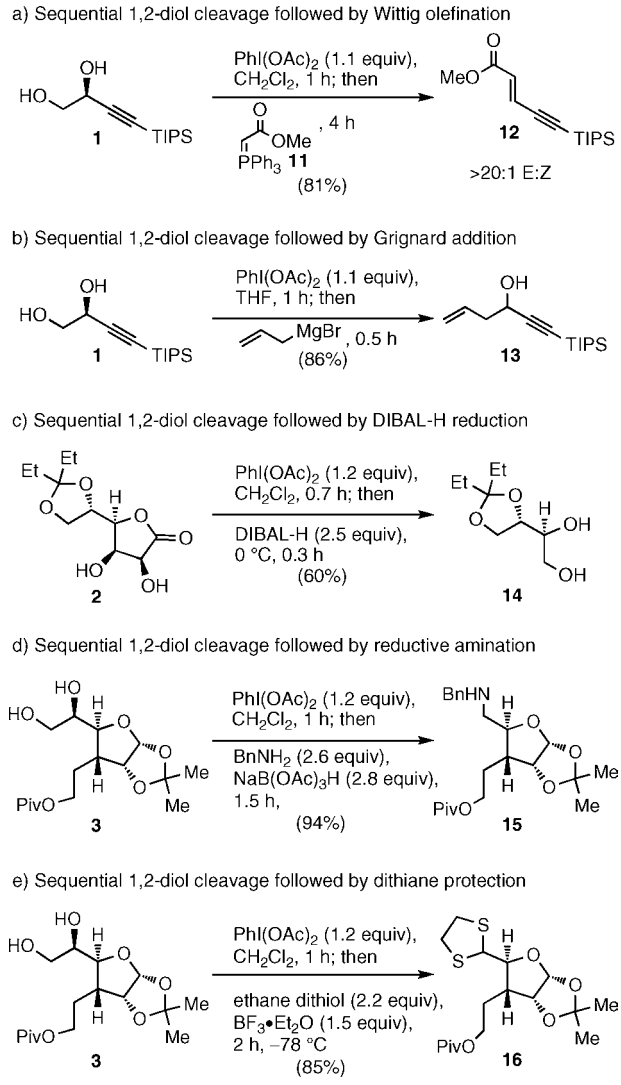
Table 1. Cleavage of 1,2-Diols to Aldehydes by $PhI(OAc)_2$[a]

entry	substrate	product	time [h]	yield [%][b]
1	 **1**	 **1a**	1	86
2	 **2**	 **2a**	1	65[c]
3	 **3**	 **3a**	0.75	99
4	 **4**	 **4a**	0.25	92
5	 **5**	 **5a**	8	99
6	 **6**	 **6a**	8	84
7	 **7**	 **7a**	2.5	97
8	 **8**	 **8a**	0.5	92
9	 **9**	 **9a**	3	95
10	 **10**	 **10a**	1	99

[a] Reactions were carried out on 100 mg scale at 0.1 M concentration in CH_2Cl_2 with 1.2 equiv of $PhI(OAc)_2$ at ambient temperature. [b] Isolated yield. [c] Competitive overoxidation observed.

(6) Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824–3825.
(7) Miyamoto, K.; Sei, Y.; Yamaguchi, K.; Ochiai, M. *J. Am. Chem. Soc.* **2009**, *131*, 1382–1383.
(8) Criegee, R.; Beucker, H. *Ann. Chem.* **1939**, *541*, 218–238.
(9) (a) Lena, J. I. C.; Fernandez, E. M. S.; Ramani, A.; Birlirakis, N.; Barrero, A. F.; Arseniyadis, S. E. *Eur. J. Org. Chem.* **2005**, 683–700. (b) Finet, L.; Lena, J. I. C.; Kaoudi, T.; Birlirakis, N.; Arseniyadis, S. *Chem.—Eur. J.* **2003**, *9*, 3813–3820. (c) Corbu, A.; Gauron, G.; Castro, J. M.; Dakir, M.; Arseniyadis, S. *Tetrahedron: Asymmetry* **2008**, *19*, 1730–1743. See also: Ohno, M.; Oguri, I.; Eguchi, S. *J. Org. Chem.* **1999**, *64*, 8995–9000. Hong, Z.; Liu, L.; Sugiyama, M.; Fu, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 8352–8353.
(10) Chen, F.-E.; Xie, B.; Zhang, P.; Zhao, J.-F.; Wang, Hui.; Zhao, L. *Synlett* **2007**, 619–622.
(11) According to SciFinder Scholar v.2007, the original article (ref 8) was cited in only 17 publications at the time this manuscript was prepared.

Scheme 3. One-Pot Applications of $PhI(OAc)_2$ Cleavage of 1,2-Diols



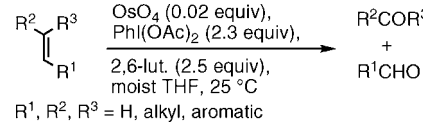
1−10). In all the examples studied, a clean conversion of the diol into the corresponding aldehydes/ketones was observed. Experimentally, the procedure involves mixing of the substrate and $PhI(OAc)_2$ in CH_2Cl_2 at room temperature, and upon completion, the product could conveniently be isolated in pure form by removal of the solvent and chromatography.[12,13]

Importantly, the $PhI(OAc)_2$-based diol cleavage strategy offers an opportunity for further reactions of the resulting carbonyl compounds in the same pot. Thus, as shown in Scheme 3a, addition of the stabilized phosphorane **11** to the resulting mixture of the cleavage of diol substrate **1** led to the isolation of conjugated ester **12** in high overall yield (81%). Likewise, Grignard addition to the same aldehyde produced propargylic alcohol **13** in 86% overall yield (Scheme 3b). On the other hand, addition of DIBAL-H to the resulting mixture of the cleavage of diol substrate **2** led to isolation of diol **14** in 60% overall yield for the one-pot sequence (Scheme 3c). Finally, reductive amination[14] (Scheme 3d) and dithiane protection (Scheme 3e) were also achieved in high yields (94% and 85%, respectively) by adding the indicated reagents to the aldehyde generated in situ from 1,2-diol **3** according to the conditions of Table 1. Additional such sequential reactions are envisioned, thus making this technology potentially appealing for applications in a variety of situations.

We then proceeded to explore the usefulness of $PhI(OAc)_2$ in cleaving olefinic bonds in the presence of catalytic amounts of OsO_4 and 2,6-lutidine. As shown in Scheme 4 and Table 2, this reaction works well in most instances (Table 2, entries 1−6), but fails to go to completion or leads to byproduct, namely α-hydroxy ketones in certain cases (Table 2, entries 7−10). It should be noted that such byproducts are also observed under Johnson−Lemieux conditions.[3]

From a more practical perspective, we discovered that a one-pot combination of dihydroxylation using Upjohn conditions followed by diol cleavage with $PhI(OAc)_2$ was a superior method to cleave olefins (Scheme 5 and Table 3, entries 1−10). Thus, treating olefins with NMO and 2,6-lutidine in the presence of catalytic OsO_4 in acetone/water (ca. 10:1) followed by the addition of $PhI(OAc)_2$ effected the cleavage of olefinic bonds in one pot to give the corresponding carbonyl compounds. This process obviously proceeds through the corresponding diol and liberates 2 molar equiv of AcOH and 1 molar equiv of PhI, both of which can be removed easily on workup and chromatography, respectively.

Scheme 4. Oxidative Cleavage of Olefins to Aldehydes and/or Ketones with $PhI(OAc)_2$ and OsO_4 (cat.) in the Presence of 2,6-Lutidine



The $PhI(OAc)_2$−NMO−OsO_4 protocol leads to aldehydes and ketones in high yields and admirably avoids the formation of the α-hydroxy ketone side products (compare Table 2, entries 9 and 10, with Table 3, entries 5 and 6). Notably, epoxides (entry 2, Table 3) survive these oxidative cleavage conditions compared with conditions that employ sodium periodate, which lead to oxidative cleavage of the epoxide moiety.[15] The reaction accommodates both cyclic and acyclic olefins as well as mono-, di-, and trisubstituted alkenes.

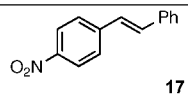
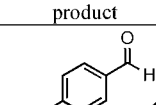
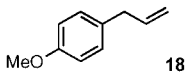
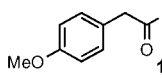
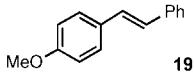
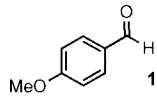
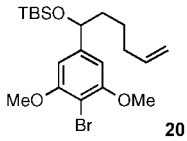
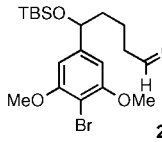
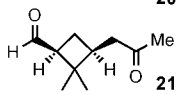
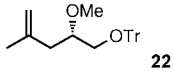
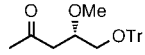
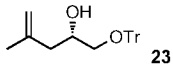
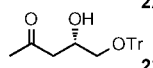
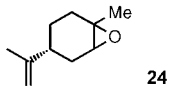
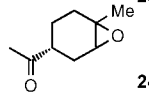
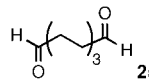
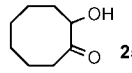
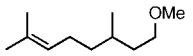
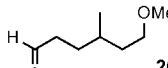
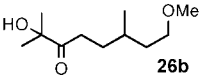
(12) The original report (ref 8) focused on the kinetics of the reaction rather than its preparative usefulness and employed AcOH or benzene as solvent.

(13) The only byproduct visible by TLC is iodobenzene.

(14) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.

(15) Binder, C. M.; Dixon, D. D.; Almaraz, E.; Tius, M. A.; Singaram, B. *Tetrahedron Lett.* **2008**, *49*, 2764–2767.

Table 2. Oxidative Cleavage of Olefins to Aldehydes and/or Ketones with $PhI(OAc)_2$ and OsO_4 (cat.) in the Presence of 2,6-Lutidine[a]

entry	substrate	product	time [h]	yield [%][b]
1	 **17**	 **17a**	9	98
2	 **18**	 **18a**	8	97
3	 **19**	 **19a**	1	98
4	 **20**	 **20a**	6	68
5	 **21**	 **21a**	24	81
6	 **22**	 **22a**	1.5	89
7	 **23**	 **23a**	18	41[c]
8	 **24**	 **24a**	48	46[d]
9	 **25**	 **25a**	0.75	7
		 **25b**		68[e]
10	 **26**	 **26a**	0.25	10
		 **26b**		70

[a] Reactions were carried out on 100 mg scale at 0.1 M concentration in THF with 0.1 mL of H_2O, 2.3 equiv of $PhI(OAc)_2$, 2.5 equiv of 2,6-lutidine, and 0.02 equiv of OsO_4 at ambient temperature. [b] Isolated yield. [c] 67% yield based on 60% conversion. [d] 49% based on 93% conversion. [e] Inseparable mixture; ratio by ^1H NMR.

The described synthetic methods offer a convenient, robust, and economical[16] alternative to the traditional olefin cleavage methods for laboratory operations. In addition to achieving high yields in most cases, all the protocols described here involve essentially homogeneous media, endowing them with certain advantages over the hetrogeneous Johnson−Lemieux-type oxidations.

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(16) NMO, $NaIO_4$, and $PhI(OAc)_2$ are all relatively inexpensive reagents (~$1−2/gram).

Scheme 5. Cleavage of Olefins to Aldehydes and/or Ketones by NMO, OsO_4 (cat.)/$PhI(OAc)_2$ in the Presence of 2,6-Lutidine

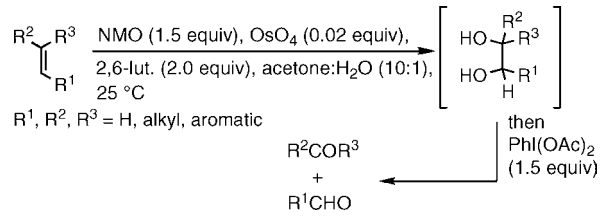
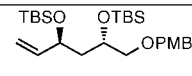
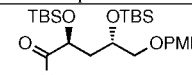
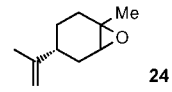
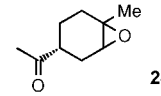
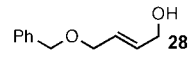
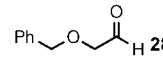
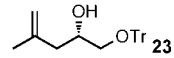
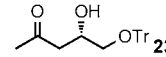
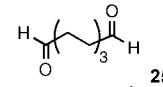
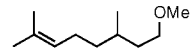
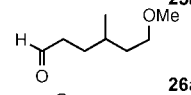
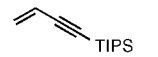
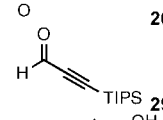
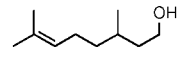
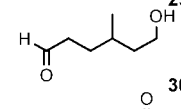
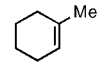


Table 3. Cleavage of Olefins to Aldehydes and/or Ketones by NMO, OsO_4 (cat.)/$PhI(OAc)_2$ in the Presence of 2,6-Lutidine[a]

entry	substrate	product	time [h]	yield [%][b]
1	 **27**	 **27a**	20	87
2	 **24**	 **24a**	2	89
3[c]	 **28**	 **28a**	6	75
4	 **23**	 **23a**	8	90
5	 **25**	 **25a**	3.5	90
6	 **26**	 **26a**	3.5	83
7	 **29**	 **29a**	20	83
8	 **30**	 **30a**	8	83
9[d]	 **31**	**31a**	0.8	79
10[d]	**32**	**32a**	1	76

[a] Reactions were carried out on 100 mg scale at 0.1 M concentration in 10:1 acetone/H_2O with 2.0 equiv of 2,6-lutidine, 1.5 equiv of NMO, 0.02 equiv of OsO_4, 1.5 equiv of $PhI(OAc)_2$ at ambient temperature. [b] Isolated yield. [c] 2.2 equiv of $PhI(OAc)_2$ was used. [d] Carried out on 1 mmol scale.

Supporting Information Available: Experimental procedures, characterization, and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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