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Palladium-Catalyzed Saegusa−Ito Oxidation: Synthesis of α,β-Unsaturated Carbonyl Compounds from Trimethylsilyl Enol Ethers

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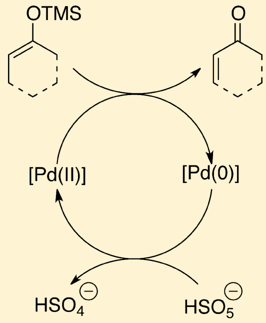
Supporting Information

ABSTRACT: Palladium-catalyzed Saegusa−Ito oxidation of trimethylsilyl enol ethers is possible using Oxone as a stoichiometric oxidant and sodium hydrogen phosphate as a buffer. Cyclic and acyclic enones as well as α,β-unsaturated aldehydes are obtained in good to excellent yields.



There is significant interest in the synthesis of α,β-unsaturated carbonyl derivatives because of their importance as building blocks in organic synthesis[1−6] and as key components of biologically active compounds.[7] As a result, numerous protocols have been developed for the preparation of α,β-unsaturated carbonyl derivatives.[8−10] Among them, the α,β-dehydrogenation of saturated carbonyl compounds is a powerful tool for the synthesis of such unsaturated compounds.[11−15] Various procedures using catalytic amounts of palladium salts and cheap green oxidants have recently appeared in the literature.[16−18] Although significant progress has been achieved, the direct oxidative formation of enones still suffers from a lack of regiochemical control when performed with unsymmetrical ketones. Conversely regiospecific enone synthesis is possible when using an enol intermediate, such as in the Saegusa−Ito oxidation.[19] The palladium-mediated oxidation of silyl enol ethers to form the corresponding α,β-unsaturated carbonyl products is a widely used reaction in total synthesis.[20−27] The major drawback of the standard Saegusa−Ito oxidation procedure is that often a superstoichiometric amount of palladium(II) acetate is necessary to obtain a satisfactory yield. Alternative procedures employing catalytic amounts of a palladium(II) complex have appeared in the literature. In their original communication, Saegusa and Ito disclosed the use of 50 mol % of palladium(II) acetate in the presence of benzoquinone.[19] A few years later, Larock and co-workers reported the use of 10 mol % of palladium(II) acetate in DMSO under an oxygen atmosphere.[28] Alternatively, the conversion of TIPS-enol ethers with 5 mol % of palladium(II) hydroxide in the presence of 5 equiv of *tert*-butylhydroperoxide was achieved by Corey and co-workers.[29] The oxidation of allyl enol carbonates was also reported to proceed using catalytic amounts of $Pd(OAc)_2$ and diphenylphosphinoethane.[30−32] Alternative organic oxidants have also been disclosed to perform the oxidation of silyl enol ethers to produce enones, namely the complex 2-iodoxybenzoic acid•4-methoxypyridine-*N*-oxide (IBX•MPO)[33] and aza-adamantane-derived oxoammonium salts (TBS-enol ethers must be used in the latter case).[34] Many of these alternative catalytic procedures are performed in DMSO, which is not always a suitable solvent for hydrophobic organic molecules.[34] Furthermore, it was recently reported that oxygen gas solubility in DMSO is very low compared to other typical solvents.[35] It appears that a general method using a cheap, readily available stoichiometric oxidant in another solvent other than DMSO remains unreported. Herein, we wish to report the use of readily available Oxone as a stoichiometric oxidant for converting trimethylsilyl enol ethers into α,β-unsaturated ketones and aldehydes in the presence of a catalytic amount of palladium(II) acetate in acetonitrile.

We first studied the oxidation of cyclohexanone trimethylsilyl enol ether (**1a**) to cyclohexenone (**2a**) using 20 mol % of palladium(II) acetate and a stoichiometric amount of Oxone, under various reaction conditions (Table 1). We first noticed that the yield improved when the reaction was run under an oxygen atmosphere, compared to ambient air (entries 1−2). In the absence of any base however, only low yields of the desired product were observed even in the presence of 3 equiv of Oxone (entries 1−2). We noticed that the major side product of the reaction was cyclohexanone, which resulted from the hydrolysis of the starting trimethylsilyl enol ether. Similar hydrolysis products have been previously observed even with more stable triisopropylsilyl enol ethers in a different catalytic system and were prevented by using inorganic bases.[29] Thus,

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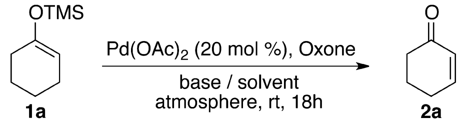
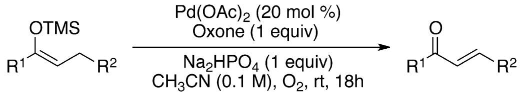
Table 1. Palladium-Catalyzed Saegusa−Ito Oxidation using Oxone as Stoichiometric Oxidant

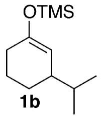
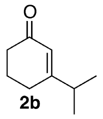
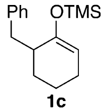
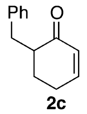
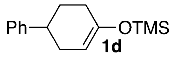
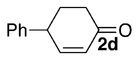
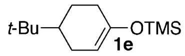
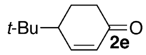
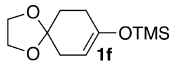
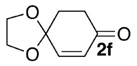
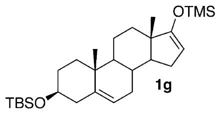
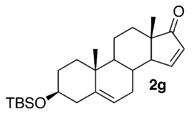
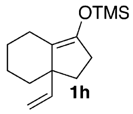
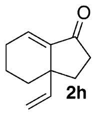
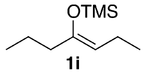
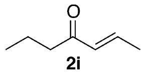
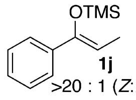
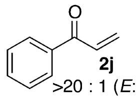
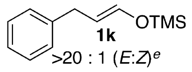
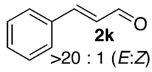


Entry[a]	Oxone (equiv)	Base (equiv)	Conditions	Yield (%)[b]
1	3	–	ACN (0.1 M), air	33
2	3	–	ACN (0.1 M), O_2	49
3	3	K_2HPO_4 (1)	ACN (0.1 M), air	56
4	3	K_2HPO_4 (1)	ACN (0.1 M), O_2	81
5	3	Na_2HPO_4 (1)	ACN (0.1 M), O_2	74
6	**1**	**Na_2HPO_4 (1)**	**ACN (0.1 M), O_2**	**92**
7	1	Na_2HPO_4 (2)	ACN (0.1 M), O_2	66
8	1	Na_2HPO_4 (1)	ACN (0.1 M), O_2	49[c]
9	1	MgO (1)	ACN (0.1 M), O_2	83
10	1	$NaHCO_3$ (1)	ACN (0.1 M), O_2	74
11	1	KOAc (1)	ACN (0.1 M), O_2	10
12	1	Na_2CO_3 (1)	ACN (0.1 M), O_2	32
13	1	K_3PO_4 (1)	ACN (0.1 M), O_2	22
14	1	Na_2HPO_4 (1)	DMF (0.1 M), O_2	86
15	1	Na_2HPO_4 (1)	DCM (0.1 M), O_2	36
16	1	Na_2HPO_4 (1)	DMSO (0.1 M), O_2	9
17	1	Na_2HPO_4 (1)	toluene (0.1 M), O_2	5

[a] Reaction performed on a 0.50 mmol scale. [b] Yields determined by GC-MS. [c] Using 10 mol % of $Pd(OAc)_2$

Table 2. Synthesis of α,β-Unsaturated Carbonyl Compounds from Trimethylsilyl Enol Ethers Using Oxone as the Stoichiometric Oxidant



Entry[a]	Substrate	Product	Yield (%)[b]
1	 **1b**	 **2b**	82[c]
2	 **1c**	 **2c**	65
3	 **1d**	 **2d**	85
4	 **1e**	 **2e**	65
5	 **1f**	 **2f**	66
6	 **1g**	 **2g**	63[d]
7	 **1h**	 **2h**	78
8	 **1i** >20 : 1 (Z:E)[e]	 **2i** >20 : 1 (E:Z)[e]	74
9	 **1j** >20 : 1 (Z:E)[e]	 **2j** >20 : 1 (E:Z)[e]	56[d]
10	 **1k** >20 : 1 (E:Z)[e]	 **2k** >20 : 1 (E:Z)[e]	69

[a] Reaction performed on a 0.50 mmol scale. [b] Isolated yields. [c] Oxone was added in two portions. [d] Reaction performed at 45 °C. [e] Determined by ^1H NMR.

we tested inorganic bases that could effectively buffer the strongly acidic Oxone and prevent the undesired hydrolysis reaction. Gratifyingly the yields were improved to 81% by adding 1 equiv of dipotassium hydrogen phosphate (K_2HPO_4) (entry 4). As was observed previously, running the reaction under an oxygen atmosphere was beneficial, although the exact role of oxygen in the process using Oxone remains to be elucidated (entries 3−4). The rest of the investigations were performed using an oxygen atmosphere. No hydrolyzed product was observed with either dipotassium or disodium hydrogen phosphate; however we noticed overoxidized products in the crude reaction mixture, indicating that an excess of the oxidant is unnecessary. To our delight, a 92% yield of cyclohexenone was obtained by lowering the amount of Oxone to 1 equiv and using disodium hydrogen phosphate (Na_2HPO_4) (entry 6). Using an excess of Na_2HPO_4 afforded the desired product with lower yields (entry 7). Unfortunately it was not possible to lower the catalyst loading, as only a 49% yield was observed when the reaction was carried out in the presence of 10 mol % of palladium(II) acetate (entry 8). While moderate yields were observed when using either magnesium oxide or sodium bicarbonate (entries 9−10), other bases such as KOAc, Na_2CO_3,[36] and K_3PO_4 afforded low yields only (entries 11−13). Overall no other base proved as good as Na_2HPO_4. A good yield was obtained with DMF as a solvent, while DCM, DMSO, and toluene all gave low yields (entries 14−17). Acetonitrile remained the most efficient solvent for the reaction.

The optimal reaction conditions, using 20 mol % of palladium(II) acetate, a stoichiometric amount of Oxone, and Na_2HPO_4 in acetonitrile under an oxygen atmosphere, were tested with various trimethysilyl enol ethers (Table 2). Nonsymmetrical cyclic enones were produced in good yields: only one regioisomer was observed, even when others could form more stable double bonds as with substrate **1c** (entries 1−2).[37] Other cyclohexenones were also produced in good yields, and the reaction was compatible with a cyclic acetal (entries 2−5). Our reaction conditions could also be used to produce cyclopentenone derivatives, as steroid-derived enone **2g** (entry 6). Trimethylsilyl enol ether **1h** was smoothly converted into enone **2h**, a key intermediate in the total synthesis of pleuromutilin (entry 7).[38]

The catalytic Saegusa−Ito reaction conditions are also compatible with the synthesis of acyclic *E*-enone **2i** from *Z*-

enol ether **1i** (entry 8).[39] Terminal alkenes could also be synthesized when the reaction was performed at 45 °C in a moderate yield (entry 9). The reaction conditions also allowed the formation of a conjugated aldehyde in a good yield (entry 10).

In conclusion, we have developed new Saegusa–Ito reaction conditions using Oxone as the stoichiometric oxidant. Both cyclic and acyclic trimethylsilyl enol ethers could be effectively converted to the corresponding enones under these reaction conditions, providing a useful process for α,β-unsaturated ketone synthesis.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all the nonaqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[40] All glassware was stored in the oven and/or was flame-dried prior to use under an inert atmosphere of gas. All oxidation reactions were performed under oxygen. Trimethylsilyl ethers were prepared using literature procedures.[41] Acetonitrile and other solvents were obtained from a solvent filtration purification system. Analytical thin layer chromatography (TLC) was performed using 0.25 mm silica gel 60-F plates. Visualization of the developed chromatograms was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, iodine, or aqueous potassium permanganate. Flash chromatography was performed using Silica Gel 60 (230–400 mesh) with the indicated solvent system according to a standard technique.[42] Melting points are uncorrected. Infrared spectra are reported in reciprocal centimeters (cm^{-1}). Chemical shifts for ^1H NMR spectra are recorded in parts per million (ppm) on the δ scale relative to an internal standard of residual solvent (chloroform, δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, and br = broad), coupling constant in Hz, integration, and assignment. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.23 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. Analytical gas chromatography (GLC) was carried out on a gas chromatograph equipped with a split mode capillary injector and a flame ionization detector. Unless otherwise noted, injector and detector temperatures were 250 °C and the carrier gas was hydrogen.

Typical Procedure for the Palladium-Catalyzed Saegusa–Ito Oxidation Using Oxone as Stoichiometric Oxidant. The trimethylsilyl ether (0.50 mmol), Na_2HPO_4 (71.0 mg, 0.50 mmol), oxone (307 mg, 0.50 mmol), and $Pd(OAc)_2$ (22.5 mg, 0.1 mmol) were weighed in a 4 dram vial, and then dry acetonitrile (5 mL) was added. The mixture was then purged with oxygen 3 times and stirred at room temperature for 18 h under an oxygen atmosphere. After filtration through Celite, the solvent was removed by vacuum and the residue was purified by silica gel chromatography. Yields as well as physical and spectroscopic data follow.

*3-Isopropylcyclohex-2-enone (**2b**).* Colorless liquid. 82% yield. All physical and spectroscopic data were identical to those previously reported.[43]

*6-Benzylcyclohex-2-enone (**2c**).* Colorless liquid. 65% yield. All physical and spectroscopic data were identical to those previously reported.[44]

*4-Phenylcyclohex-2-enone (**2d**).* Colorless liquid. 85% yield. All physical and spectroscopic data were identical to those previously reported.[45]

*4-tert-Butylcyclohex-2-enone (**2e**).* Colorless liquid. 65% yield. All physical and spectroscopic data were identical to those previously reported.[16]

*1,4-Dioxaspiro[4.5]dec-6-en-8-one (**2f**).* Colorless liquid. 66% yield. All physical and spectroscopic data were identical to those previously reported.[46]

*(3S,10R,13S)-3-(tert-Butyldimethylsilyloxy)-10,13-dimethyl-1,3,4,7,8,9,10,11,12,13-decahydro-2H-cyclopenta[a]phenanthren-17(14H)-one (**2g**).* The trimethylsilyl ether (0.50 mmol), Na_2HPO_4 (71.0 mg, 0.50 mmol), oxone (307 mg, 0.50 mmol), and $Pd(OAc)_2$ (22.5 mg, 0.1 mmol) were weighed in a 4 dram vial, and then dry acetonitrile (5 mL) was added. The mixture was then purged with oxygen 3 times and stirred at 45 °C for 18 h under an oxygen atmosphere. After filtration through Celite, the solvent was removed by vacuum and the residue was purified by recrystallization in ethyl acetate/pentane. White crystalline solid. 63% yield. Mp 99–101 °C. (lit.: 110–112 °C (hexane)).[47] All spectroscopic data were identical to those previously reported.[47]

*3a-Vinyl-2,3,3a,4,5,6-hexahydroinden-1-one (**2h**).* Colorless liquid. 78% yield. All physical and spectroscopic data were identical to those previously reported.[16]

*(E)-Hept-2-en-4-one (**2i**).* Colorless liquid. 74% yield. All physical and spectroscopic data were identical to those previously reported.[48]

*1-Phenylprop-2-en-1-one (**2j**).* The trimethylsilyl ether (0.50 mmol), Na_2HPO_4 (71.0 mg, 0.50 mmol), oxone (307 mg, 0.50 mmol), and $Pd(OAc)_2$ (22.5 mg, 0.1 mmol) were weighed in a 4 dram vial, and then dry acetonitrile (5 mL) was added. The mixture was then purged with oxygen 3 times and stirred at 45 °C for 18 h under an oxygen atmosphere. After filtration through Celite, the solvent was removed by vacuum and the residue was purified by silica gel chromatography. Colorless liquid. 56% yield. All physical and spectroscopic data were identical to those previously reported.[49]

*E-Cinnamaldehyde (**2k**).* Colorless liquid. 69% yield. Commercially available product: all physical and spectroscopic data were identical to those previously reported.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization spectra (^1H and ^{13}C NMR) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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