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$Pd(OH)_2$/C-Mediated Selective Oxidation of Silyl Enol Ethers by *tert*-Butylhydroperoxide, a Useful Method for the Conversion of Ketones to α,β-Enones or β-Silyloxy-α,β-enones

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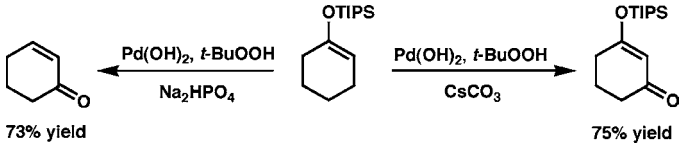
ABSTRACT



$Pd(OH)_2$-catalyzed oxidation of silyl enol ethers by *t*-BuOOH gives either β-silyloxy-α,β-enones or α,β-enones in good yields depending on the base used.

Exploration of the oxidation of silyl enol ethers under a variety of conditions has led to a number of synthetically valuable transformations.[1] The formal 1,4-dehydrosilation reaction using either $Pd(OAc)_2$/benzoquinone[2] or iodoxybenzoic acid (IBX) leading to the formation of α,β-enones[3] has proven to be especially useful in synthesis. Recently, we described a novel allylic oxidation of olefins using *t*-BuOOH in the presence of $Pd(OAc)_2$, Pd/C, or $Pd(OH)_2$, which provides a catalytic method for the synthesis of either α,β-enones or 1,4-enediones.[4,5] We report herein the application of this catalytic system with an added base to the oxidation of triisopropylsilyl enol ethers of ketones to form selectively either β-keto enol silyl ethers or α,β-enones depending on the base used.

The triisopropylsilyl (TIPS) group was selected as the protecting group for the enol ether substrates due to its stability under the required reaction conditions. Cyclohexanone triisopropylsilyl ether (**1**) was initially subjected to our oxidation conditions using 5 equiv of *t*-BuOOH, 5% mol 20% $Pd(OH)_2$ on carbon (Pearlman's catalyst; Aldrich Co.), and 1 equiv of K_2CO_3 in methylene chloride at 4 °C. The reaction mixture was analyzed by ^1H NMR after 48 h, which showed a 2:1 ratio of the β-keto enol silyl ether from

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(1) See: (a) Stankovic, S.; Espenson, J. H. *J. Org. Chem.* **1998**, *63*, 4129. (b) Adam, W.; Fell, R. T.; Saha-Moller, C. R.; Zhao, C. G. *Tetrahedron: Asymmetry* **1998**, *9*, 397. (c) Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 708. (d) Ryter, K.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 2658. (e) Yamamoto, H.; Tsuda, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 7174.

(2) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(3) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996.

(4) (a) Yu, J. Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727. (b) Yu, J. Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232.

(5) Also, for a recent example of Rh(I)-catalyzed allylic oxidation by *t*-BuOOH, see: Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622.

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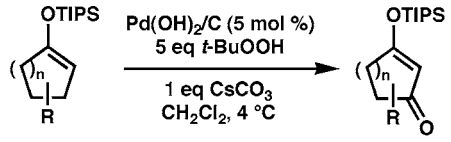
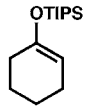
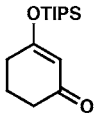
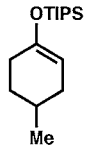
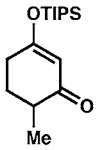
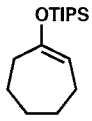
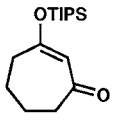
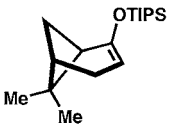
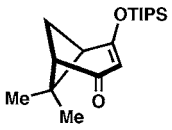
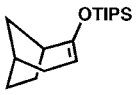
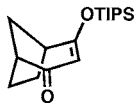
allylic oxidation and cyclohexanone (from simple hydrolysis). Presumably, the in situ-generated water caused the hydrolysis of the silyl enol ether. It was found that the combined use of a different base, Cs_2CO_3, and 1 atm of molecular oxygen increased the rate of oxidation and minimized hydrolysis to ketone. Under these optimized conditions, a variety of the silyl enol ether substrates were oxidized in good yields to give the corresponding β-keto enol silyl ethers as shown in Table 1.

Table 1. Synthesis of β-Keto Enol Silyl Ethers

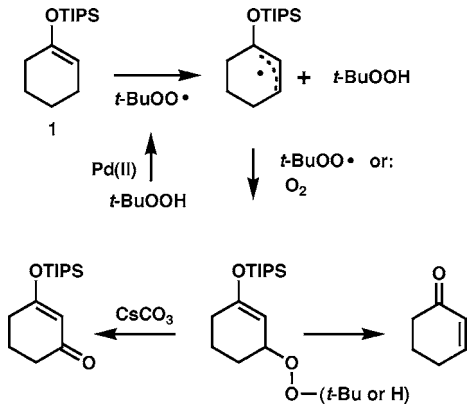


entry	substrate	product	time (h)	yield, %
1			38	75
2			32	65
3			32	62
4			48	70
5			48	76

β-Keto enol ethers have been widely used as key intermediates in organic synthesis.[6] The most common method for the synthesis of β-keto enol ethers, O-alkylation of cyclic β-diketone enolates, suffers from competition of O- vs C-alkylation and from regiochemical issues in the case of nonsymmetric substrates. Zubaidha recently communicated another procedure for the direct etherification of cyclic β-ketones with alcohols mediated by iodine.[7] We believe that this two-step-sequence converting simple ketones into β-keto enol silyl ethers provides a valuable transformation for organic synthesis since it starts from readily available ketones and since it is regioselective. This method also allows ready access to chiral β-keto enol silyl ethers by use of chiral ketone precursors (see Table 1, entries 4 and 5).[8,9]

On the basis of the mechanistic investigations previously reported,[4] the likely reaction pathway is that outlined in Scheme 1.

Scheme 1



In principle, the allylic peroxide intermediate could also undergo elimination of the *tert*-butylperoxy and TIPS groups to form an α,β-enone (Scheme 1). In fact, we find that the oxidation of the β-keto enol silyl ether **1** in the presence of a milder base (Na_2HPO_4) gives the corresponding α,β-enone as the main product. The oxidation of a series of β-keto enol silyl ethers in the presence of molecular oxygen at 24 °C gave α,β-enones in good yields as shown in Table 2. It is noteworthy that in the case of entry 6 of Table 2, the

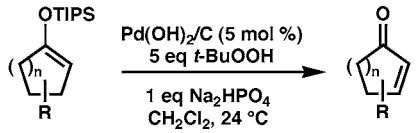
(6) See: (a) Zhang, Y.; Raines, A. J.; Flowers, R. A., II. *Org. Lett.* **2003**, *5*, 2363. (b) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1963**, *28*, 27. (c) Takahashi, K.; Tanaka, T.; Suzuki, T.; Hirama, M. *Tetrahedron* **1994**, *50*, 1327.

(7) Bhosale, R. S.; Bhosale, S. V.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. *Tetrahedron Lett.* **2004**, *45*, 7187.

(8) **General Procedure for the Preparation of Silyl Enol Ethers.** Triisopropylsilyl triflate (1.84 g, 6.0 mmol) was added to a solution of the ketone (5.0 mmol) and triethylamine (0.91 g, 9.0 mmol) in dichloromethane (15 mL). The progress of the reaction was monitored by TLC, and when the reaction was complete, the mixture was diluted with dichoromethane and washed with cold sodium bicarbonate. After the organic layer was dried over anhydrous sodium sulfate and concentrated on a rotovap, the residue was taken up in dry ether and separated from the insoluble triethylammonium triflate. The ether solution was then concentrated and chromatographed on basic alumina (pH 9.0−9.5) using pure hexane as an eluent to give the pure product.

(9) **General Procedure for the Synthesis of β-Silyloxy-α,β-enones.** A 25 mL round-bottom flask equipped with a stir bar was charged under air with $Pd(OH)_2/C$ (20% Pd) (8.5 mg, 0.016 mmol), Cs_2CO_3 (104 mg, 0.32 mmol), CH_2Cl_2 (1 mL), and silyl enol ether (0.32 mmol). The mixture was cooled to 4 °C with an ice bath, and *tert*-butylhydroperoxide (TBHP) (160 μL, 1.6 mmol) was added with vigorous stirring. The flask was purged with pure oxygen gas and kept under an oxygen atmosphere with a balloon. The mixture was stirred at 4 °C for the time indicated in Table 1 (reaction complete as indicated by TLC analysis). The reaction mixture was then filtered through a short pad of silica gel and washed with CH_2Cl_2. After removal of the solvent by rota-evaporation at 24 °C, the crude product was purified by flash column chromatography (ether−hexane, 1:1) to provide the analytically pure sample as a clear oil.

Table 2. Synthesis *o*f α,*β*-Enones



entry	substrate	product	time (h)	yield, %
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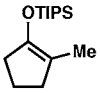
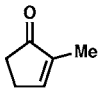
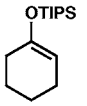
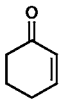
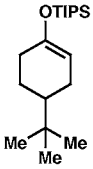
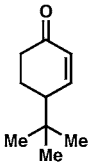
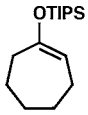
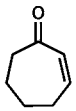
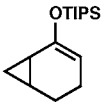
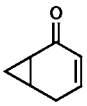
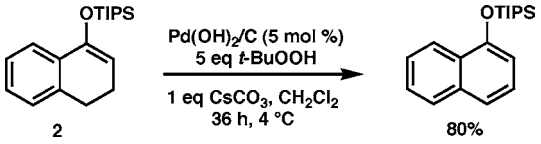
2			48	72
3			42	73
4			48	86
5			44	74
6[a]			72	70

[a] Triethylamine as base.

cyclopropane unit survived this radical oxidation process, an indication that the reaction of the allylic radical with the molecular oxygen or *t*-BuOO• is fast relative to cleavage of the three-membered ring. $Pd(OAc)_2$-catalyzed oxidation of silyl enol ethers by benzoquinone has been previously reported by Saegusa and proposed to involve an oxo-π-allylpalladium complex as a key intermediate.[2] In contrast, the oxidation reaction described herein is clearly a radical process as shown in Scheme 1.[4] The present methodology can also be applied to aromatization of dihydroaromatic substrates as shown by the oxidation of **2** to the TIPS ether of α-naphthol (Scheme 2).[10]

Scheme 2



In summary, the Pd-mediated oxidation of silyl enol ethers by *t*-BuOOH provides a simple and convenient method for the preparation of *β*-keto enol silyl ethers and α,*β*-enones from a range of ketonic starting materials.

Acknowledgment. We acknowledge the Royal Society for a Research Fellowship, the Camille and Henry Dreyfus Foundation for a New Faculty Award and Brandeis University for financial support (to J.Q.Y.).

Supporting Information Available: Experimental and characterization data for starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **General Procedure for the Synthesis of α,b-Enones.** A 50 mL round-bottom flask equipped with a stir bar was charged under air with $Pd(OH)_2/C$ (20% Pd) (17 mg, 0.032 mmol), Na_2HPO_4 (9.0 mg, 0.064 mmol), CH_2Cl_2 (2 mL), and silyl enol ether (0.64 mmol). The flask was purged with pure oxygen gas and kept under an oxygen atmosphere with a balloon. To this mixture was added *tert*-butylhydroperoxide (TBHP) (40 μL, 0.40 mmol) in four portions every 2 h with vigorous stirring. The mixture was stirred at 24 °C for the time indicated in Table 2 (reaction complete by TLC analysis). The reaction mixture was then filtered through a short pad of silica gel and washed with CH_2Cl_2. After removal of the solvent by rotaevaporation at 24 °C, the crude product was purified by flash column chromatography (ether−hexane, 1: 1) to provide the analytically pure sample as a clear oil.