J. Am. Chem. Soc. **1998,** *120,* 2658−2659

Dichloro(2,2,2-trifluoroethoxy)oxovanadium(V). A Remarkably Effective Reagent for Promoting One-Electron Oxidative Cyclization and Unsymmetrical Coupling of Silyl Enol Ethers

Kendal Ryter and Tom Livinghouse*[,1]

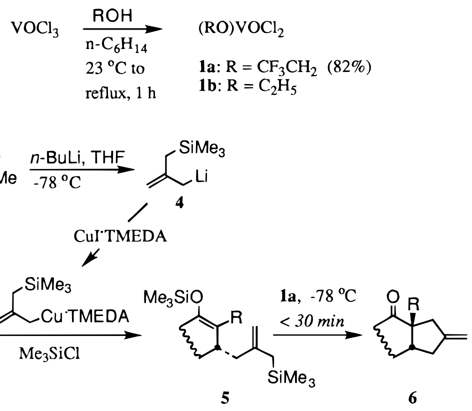
Department of Chemistry
Montana State University
Bozeman, Montana 59717

Received October 15, 1997

Bond forming reactions that involve the oxidative activation of unsaturated organic molecules have gained increasing significance as versatile synthetic methods.[2] Transition metal-based oxidants have become widely used as reagents to effect the electrophilic coupling of neutral participants in this context.[3] Among the complexes that have been used for this purpose, vanadium(V) compounds have recently gained renewed attention as reagents for the selective one-electron oxidation of β-hydroxy acids,[4] cyclobutanones,[5] and silyl enol ethers.[6] It is, however, most significant that very few of the preexisting transition metal-based reagents are capable of inducing highly efficient carbon−carbon bond formation via oxidative coupling. In this paper, we describe the synthesis of dichloro(2,2,2-trifluoroethoxy)oxovanadium(V) (**1a**), a new vanadium(V) ester which possesses an exceptionally versatile reactivity profile for the oxidative activation of silyl enol ethers, and demonstrate the utility of this reagent for methylenecyclopentannulation as well as the synthesis of unsymmetrical 1,4-diones via free radical coupling.

Reagent Development and Application to Methylenecyclopentannulation. The importance of natural products containing five-membered carbocyclic rings has stimulated considerable interest in the development of efficient procedures for cyclopentannulation. In recent years, improved versions of the Nazarov cyclization,[7a] Pauson−Khand reaction,[7b] and allenylsilane−enone [3 + 2] cycloaddition,[7c] as well as other transformations, have been reported for this purpose. In addition, Trost has developed a mechanistically intriguing procedure for methylenecyclopentannulation that relies on Pd(0) catalysis.[7d] Unfortunately, the Trost procedure often gives modest yields when cycloalkenones are used as substrates (even when the enone trap is used in excess) and has not been shown to be effective for the methylenecyclopentannulation of 2-substituted cycloalkenones. In principle, the silylative 1,4-addition of an organocopper reagent derived from [2-((trimethylsilyl)methyl)prop-2-enyl]lithium (**4**)[8] to an appropriate acceptor, followed by oxidative cyclization of the resulting silyl enol ether **5**, would constitute a very useful and synthetically complementary method for methylenecyclopentannulation.

Scheme 1



Of the various procedures that were examined for the conjugate addition of metallo derivatives of **4** to typical enones (e.g., **3a** and **3b**), a slight modification of the method of Johnson and Marren was found to be most effective.[9,10] Accordingly, sequential treatment of 2-((trimethylsilyl)methyl)-2-methylselenoprop-1-ene (**2**)[8] (1.0 equiv) with *n*-BuLi (1.0 equiv, THF, −78 °C) followed by the addition of CuI (1.0 equiv) complexed with TMEDA (3.0 equiv) in THF (−78 °C), and final addition of Me$_3$SiCl (2.5 equiv) and the enone of interest (1.0 equiv, −78 °C) provided the corresponding silyl enol ethers **5a**−**e** with excellent 1,4-addition selectivity in >90% yield. Repeated attempts to effect the oxidative cyclization of **5a** with (EtO)VOCl$_2$ (**1b**),[6a] previously regarded as the reagent of choice for the oxidative coupling of silyl enol ethers with allylsilanes, resulted in unsatisfactory conversions to the desired methylenecyclopentenones **6a** and **6b**, even after reaction times as long as 3 days at room temperature. Preactivation of **1b** by treatment with Me$_3$SiOTf,[6b] prior to the addition of the silyl enol ether, did little to improve the efficiency of cyclization. By way of contrast, the new vanadium(V) ester, (CF$_3$CH$_2$O)VOCl$_2$ (**1a**), which can be economically prepared on large scale by treatment of VOCl$_3$ with 2,2,2-trifluoroethanol (1.0 equiv), promoted remarkably efficient cyclizations of these substrates in <30 min at −78 °C (Scheme 1).[11,12] The enhanced reactivity of **1a** relative to **1b** is consistent with an increase in the electrophilicity of the active vanadium center present in this ester. The evident generality of this new reagent for effecting oxidative methylenecyclopentannulation was

---

[1] Fellow of the Japan Society for the Promotion of Science, 1997.

[2] (a) Giese, B. *Radicals in Organics Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417, 489. (c) Heiba, E. I.; Dessau, R. M. *J. Org. Chem.* **1974**, *39*, 3456. (d) Corey, E. J.; Kang, M.-C. *J. Am. Chem. Soc.* **1984**, *106*, 5384. (e) Yang, F. Z.; Trost, M. K.; Fristad, W. E. *Tetrahedron Lett.* **1987**, *28*, 1493. (f) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem Soc.* **1987**, *109*, 3152, 6551. (g) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525. (h) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014. (i) Pattenden, G. *Chem. Soc. Rev.* **1988**, *17*, 361 and references therein.

[3] Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981.

[4] Meier, I. K.; Schwartz, J. *J. Am. Chem. Soc.* **1989**, *111*, 3069.

[5] Hirao, T.; Fujii, T.; Shun-ichi, M.; Ohshiro, Y. *J. Org. Chem.* **1991**, *56*, 2264.

[6] (a) Fujii, T.; Hirao, T.; Ohshiro, Y. *Tetrahedron Lett.* **1992**, *33*, 5823. (b) Hirao, T.; Fujii, T.; Ohshiro, Y. *Tetrahedron* **1994**, *50*, 10207. (c) Hirao, T. *Chem. Rev.* **1997**, *97*, 2707 and references therein.

[7] (a) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. (b) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285. (c) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (d) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315 and references therein.

[8] Ryter, K.; Livinghouse, T. *J. Org. Chem.* **1997**, *62*, 4842.

[9] Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27.

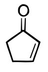
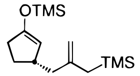
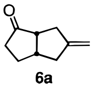
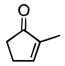
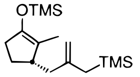
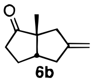
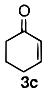
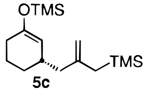
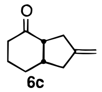
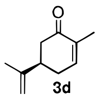
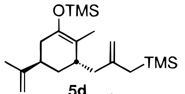
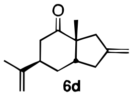
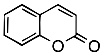
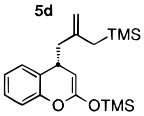
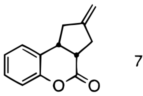
[10] Surprisingly, Cu(I) sources containing the resident (trimethylsilyl)methyl ligand proved less effective for the conjugate addition of **4** to enones. Bertz, S. H.; Eriksson, M.; Maio, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906.

[11] General procedure for oxovanadium(V)-induced cyclizations: Preparation of (2*H*)-hexahydro-5-methylene-1-pentalenone (**6a**). A 100-mL round-bottomed flask equipped with a magnetic stirring bar and septum was flame dried under a stream of argon, charged with CH$_2$Cl$_2$ (40 mL), (CF$_3$CH$_2$O)VOCl$_2$ (1.95 mL, 12 mmol) and cooled to −78 °C. A solution of silyl enol ether, **5a** (1.69 g, 6.00 mmol) in CH$_2$Cl$_2$ (5 mL) was then added via syringe pump over 30 min. The reaction mixture was stirred another 10 min. at −78 °C and poured into a separatory funnel containing aqueous HCl (1.5 M, 5 mL) and ether (30 mL). The layers were mixed and separated, and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. The oily residue was purified by chromatography on silica gel (2.5% Et$_2$O/pentane with 0.01% Et$_3$N for elution) to give pentalenone **6a** (660 mg, 82%) as a colorless oil. Spectral data were consistent with those reported in the literature.[7d]

[12] In a control experiment, the use of VOCl$_3$ proved ineffective for the oxidative activation of silyl enol ether **5a**.

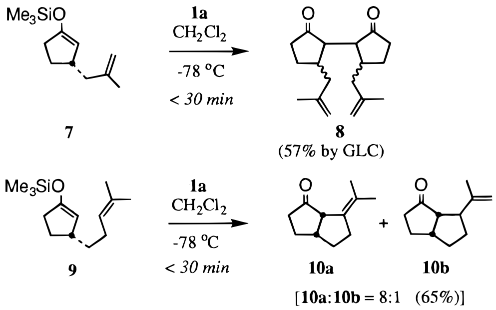
S0002-7863(97)03585-3 CCC: $15.00

Table 1. Oxidative Cyclizations of 3-[2-((Trimethylsilyl)methyl)-prop-2-enyl] Silyl Enol Ethers by $(CF_3CH_2O)VOCl_2$

Enone	Product[a]	Yield (%)[b]	Product	Yield (%)[c]
 3a	 5a	95	 6a	82[d]
 3b	 5b	90	 6b	71
 3c	 5c	90	 6c	78[d]
 3d	 5d	97	 6d	83[e]
 3e	 5e	92	 6e	73[d]

[a] Products were not fully characterized and were used immediately. [b] Yields are based on recovery of crude material, >90% pure by NMR. [c] Yield was calculated over two steps based on starting enone **3a**−**e**. [d] Spectral data were consistent with data reported in the literature.[7d] [e] Isolated as one diastereomer. The structure was confirmed by ^1H NMR NOE experiments.

Scheme 2



subsequently demonstrated for a range of α,β-unsaturated carbonyl compounds. The results of this study are presented in Table 1.

The importance of the allylically disposed trimethylsilyl substituent in facilitating the "disfavored" 5-endo-trig mode of cyclization was established by examining the behavior of silyl enol ether **7** in the presence of **1a**. Under conditions identical to those used for the cyclizations of **5a**−**e**, oxidation of **7** provided a complex mixture of products, consisting primarily of the isomeric 1,4-diketone dimers **8** (Scheme 2).[13] In a significant departure from this informative but unsatisfactory result, exposure of **9** to **1a** under the usual set of reaction conditions led to a smooth 5-exo-trig cyclization resulting in the production of the bicyclo[3.3.0]octanones **10a** and **10b** (**10a**:**10b** = 8:1) in 65% yield.[14]

The use of one-electron oxidants for the synthesis of unsymmetrical 1,4-diones from equimolar quantities of the corresponding enolate derivatives has remained an endeavor in which only modest success has been achieved. Among the various reagents that have previously been utilized for the oxidative coupling of silyl enol ethers, $(EtO)VOCl_2$ (**1b**) appears to be the most effective, despite several noteworthy limitations.[6a] The diminished ability of **1b** to promote unsymmetrical couplings involving moderately reactive partners (i.e., **11a**), even when used in excess (**11a**:**12** = 1:2), constitutes a significant preparative deficiency (Scheme 3). Accordingly, $(CF_3CH_2O)VOCl_2$ (**1a**) was examined for efficacy in a short series of oxidative couplings that were previously reported as the worst-case scenarios for **1b**.[6a] A summary of this comparative study appears in Table 2.

Scheme 3

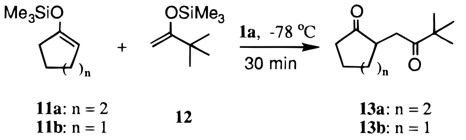
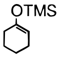
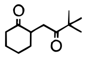
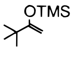
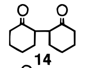
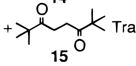
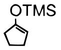
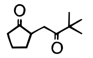
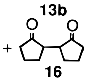


Table 2. Oxidative Coupling of Silyl Enol Ethers by $(CF_3CH_2O)VOCl_2$

Reactants	Conditions	Products	Yield (%) A[a]	B
 11a	(A)[c] $(EtO)VOCl_2$[e], -78 °C, 3h; -40 °C, 4h	 13a	40[b]	68[b]
+  12	(B) $(CF_3CH_2O)VOCl_2$[f], -78 °C, 30 min	+  14	38	2
		+  15	Trace	Trace
 11b + 12	A[c]	 13b	58[b]	75[b]
	B	+  16	32	Trace
		+ 15	Trace	0
12	A[f] B	15	Trace-11[d]	62[b]
11a	A[f] B	14	75[b]	93[b]

[a] Yields reported by Hirao, Ohshiro, and Fujii.[6a] [b] Isolated yields. All other yields were determined by GLC analysis. [c] In these reactions, 2 equiv of silyl enol ether **12** was used. [d] Only a trace of the desired product, **15**, was detected under standard conditions. Elevated temperatures (room temperature) and long reaction times were necessary to improve the yield. [e] Three equivalents of the oxovanadium reagent was used. [f] Two equivalents of the oxovanadium reagent was used.

As is evident from the results presented above, **1a** is a superb reagent for the unsymmetrical oxidative coupling of silyl enol ethers and is capable of effecting the union of equimolar quantities of reactant molecules at −78 °C in less than 30 min. Further investigation into the synthetic utility of **1a** for one-electron oxidative bond formation as well as the use of the present reactions in stereocontrolled synthesis will be reported shortly.

Acknowledgment. Financial support for this research by a grant from the National Institutes of Health is gratefully acknowledged.

Supporting Information Available: Text describing the experimental procedures, NMR spectra for **1a**, **6b**, and **6d** and spectral data for all compounds (14 pages). See any current masthead page for ordering information and Web access instructions.

JA973585E

---

(13) Compelling evidence for the formation of the isomeric 1,4-diones **8** was provided by GCMS as well as ^1H and ^{13}C NMR.

(14) For a related series of cyclizations that proceed via α-carbonyl radicals, see: Sha, C.-K.; Jean, T.-S.; Wang, D.-C. *Tetrahedron Lett.* **1990**, *31*, 3745.