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Mild and Selective Vanadium-Catalyzed Oxidation of Benzylic, Allylic, and Propargylic Alcohols Using Air

Susan K. Hanson,* Ruilian Wu, and L. A. "Pete" Silks

Chemistry and Biosciences Divisions, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, United States

skhanson@lanl.gov

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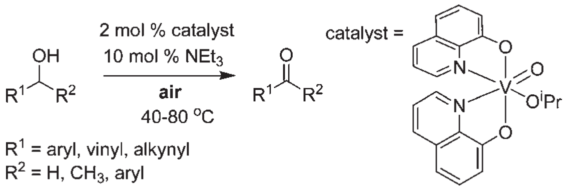
ABSTRACT



Transition metal-catalyzed aerobic alcohol oxidation is an attractive method for the synthesis of carbonyl compounds, but most catalytic systems feature precious metals and require pure oxygen. The vanadium complex $(HQ)_2V^V(O)(O^iPr)$ (2 mol %, HQ = 8-quinolinate) and NEt_3 (10 mol %) catalyze the oxidation of benzylic, allylic, and propargylic alcohols with air. The catalyst can be easily prepared under air using commercially available reagents and is effective for a wide range of primary and secondary alcohols.

The oxidation of alcohols to afford carbonyl compounds is a key reaction in synthetic organic chemistry. Recent years have seen major progress in the development of catalytic aerobic alcohol oxidation, which offers economic and environmental benefits over traditional stoichiometric oxidants.[1] Despite these advances, many reported systems feature precious metal catalysts (Pd, Ru, Ir) and use oxygen pressures of 1 atm or more.[2–4] Due to issues of scarcity and cost, there is considerable interest in replacing precious metal catalysts with earth-abundant metals.[5] Using air instead of pure oxygen is also advantageous,[6] reducing the safety hazard associated with heating organic solvents under elevated O_2 pressures.

Vanadium complexes have shown potential as base-metal catalysts for aerobic alcohol oxidation, in some cases proving effective for substrates where palladium catalysts display limited activity. For instance, vanadium is known to catalyze the selective aerobic oxidation of propargylic

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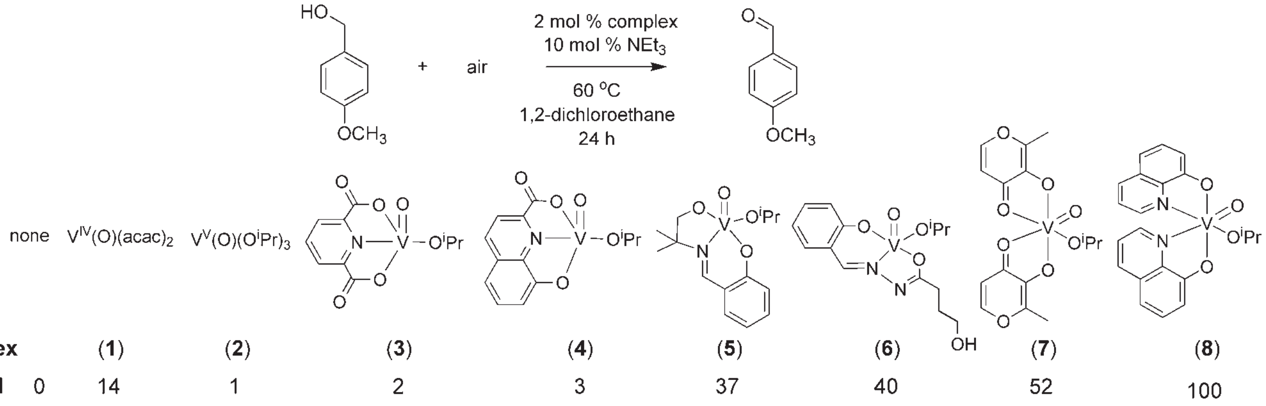
10.1021/ol103107v

Scheme 1



alcohols, a reaction using V^{IV}(O)(acac)$_2$ (1−5 mol %) and molecular sieves at 80 °C.[7] The combination of V^{IV}(O)(acac)$_2$ and DABCO (DABCO = 1,4-diazabicyclo[2.2.2]octane) also catalyzes the oxidation of benzylic and allylic alcohols in ionic liquid solvent at 80−100 °C.[8] Vanadium catalysts with chiral Schiff base ligands effect the oxidative kinetic resolution of α-hydroxyesters, amides, and phosphonates.[9−11] These reports are promising indications of the versatility of vanadium catalysts, but each requires an atmosphere of pure oxygen. Very recently, Ohde and Limberg reported a metavanadate−cinnamic acid system that catalyzes the oxidation of activated alcohols using mixtures of argon and O$_2$, but this catalyst is highly moisture sensitive.[12]

Here, we describe a vanadium-based system for the aerobic oxidation of benzylic, allylic, and propargylic alcohols. The reactions proceed under mild conditions (air, 40−80 °C) and in a variety of solvents. Moreover, the catalyst can be prepared in air using commercially available reagents, making the overall process inexpensive, simple, and accessible without the use of a drybox or Schlenk techniques.

We recently studied the mechanism of alcohol oxidation by dipicolinate vanadium(V) complexes and found that a base (pyridine) promoted alcohol oxidation.[13] Inspired by this finding, we tested the aerobic oxidation of 4-methoxybenzyl alcohol at 60 °C under air using several different vanadium complexes (2 mol %) and a base promoter (10 mol % NEt$_3$) in 1,2-dichloroethane (Scheme 1). Poor yields were observed with V^{IV}(O)(acac)$_2$, V^{V}(O)(O^{i}Pr)$_3$, and complexes of carboxylate-based ligands (dipicolinate (**3**) and 8-quinolinate-2-carboxylate (**4**)). Complexes with more electron-donating ligands displayed higher activity,[14−16] with the highest activity observed for the complex (HQ)$_2$V^{V}(O)(O^{i}Pr) (**8**) (HQ = 8-quinolinate) reported by Sawyer, Floriani, and Scheidt (Scheme 1).[17−19] Complex **8** is easily prepared in one step by the reaction of 8-hydroxyquinoline with V^{IV}(O)(acac)$_2$ under air in 2-propanol.[20]

Table 1. Solvents Tested for the Oxidation of 4-Methoxybenzyl Alcohol[a]

entry	solvent	% yield (NMR)
1	1,2-dichloroethane	99
2	ethyl acetate	91 (99)
3	toluene	78 (96)
4	THF	96 (99)
5	CH$_3$CN	93 (98)
6	CH$_2$Cl$_2$	92[b] (99)[b]
7	1,2-dichlorobenzene	99
8	2-methyl-THF	99
9	DMSO	69
10	pyridine	12

[a] Conditions: 2 mol % of **8**, 10 mol % of NEt$_3$, 60 °C, 24 h. [b] Conditions: 5 mol % of **8**, 10 mol % of NEt$_3$, 40 °C, 24 h. Values in parentheses indicate % yield after 48 h reaction time.

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(18) (a) Giacomelli, A.; Floriani, C.; Duarte, A. O. D. S.; Chiesi-Villa, A.; Guastini, C. *Inorg. Chem.* **1982**, *21*, 3310–3316. (b) Pasquali, M.; Landi, A.; Floriani, C. *Inorg. Chem.* **1979**, *18*, 2397–2400.

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(20) See the Supporting Information for details.

Encouraged by these results, we screened several different solvents for the oxidation of 4-methoxybenzyl alcohol using **8** (2 mol %) and NEt_3 (10 mol %). High yields of the aldehyde were observed after 24 h at 60 °C in THF, ethyl acetate, and acetonitrile, with $>99\%$ NMR yield observed in 1,2-dichloroethane, 1,2-dichlorobenzene, and 2-methyltetrahydrofuran (Table 1, entries 1−8).

The effect of the additive was then examined for the oxidation of 4-methoxybenzyl alcohol using **8** (2 mol %) in 1,2-dichloroethane (Table 2). Triethylamine, diisopropylethylamine, and TEMPO were all effective promoters of the vanadium complex, affording high yields of 4-methoxybenzaldehyde after 24 h at 60 °C (entries 2−5). In contrast, less than 5% yield was observed with the vanadium complex alone (no additive, entry 1), suggesting a key role for the nitrogen base.

Table 2. Additives Tested for the Oxidation of 4-Methoxybenzyl Alcohol[a]

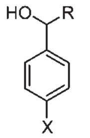
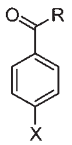
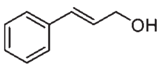
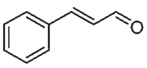
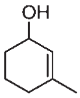
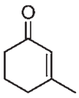
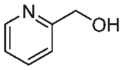
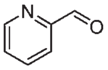
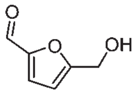
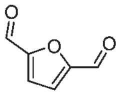
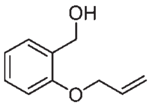
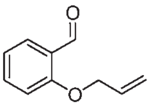
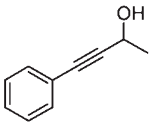
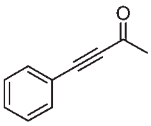
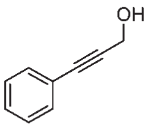
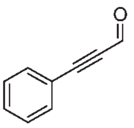
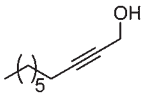
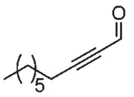
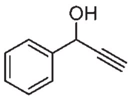
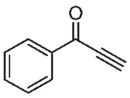
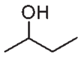
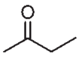
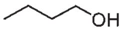
entry	additive (10 mol %)	% yield (NMR)
1	none	4
2	triethylamine	99 (49)
3	triethylamine (5 mol %)	99 (42)
4	diisopropylethylamine	99 (31)
5	TEMPO	99 (8)
6	DABCO	83
7	DMAP	28
8	NaO^{t}Bu	19
9	Na_2CO_3	16
10	DBU	5
11	proton sponge	6
12	NaOAc	1

[a] Conditions: 2 mol % of **8**, 10 mol % of additive, 1,2-dichloroethane solvent, 60 °C, 24 h. Values in parentheses indicate % yield after 4 h reaction time.

The substrate scope of the alcohol oxidation was investigated using **8** (2 mol %) and NEt_3 (10 mol %) in 1,2-dichloroethane (Table 3). A range of benzylic alcohols were oxidized and the aldehydes or ketones isolated in high yields (entries 1−8). Steric bulk around the alcohol slowed the reaction, with the more hindered α-isopropyl- and α-*tert*-butyl benzyl alcohols showing only 20 and 0% yield, respectively (entries 7 and 8). Cinnamyl alcohol, 3-methyl-2-cyclohexen-1-ol, 5-hydroxymethylfurfural (HMF), and 2-hydroxymethylpyridine were oxidized to the corresponding aldehyde or ketone in high yields (entries 9−12).

2-Allyloxybenzylalcohol has been used by Galli and coworkers as a substrate probe in catalytic oxidations to detect the intermediate formation of a carbon-based radical, which has been reported to undergo an intramolecular ring closure as shown in Scheme 2.[21,22] This substrate was oxidized to the corresponding aldehyde in 95% isolated yield (entry 13); none of ring-closed product **A** was detected by ^{1}H NMR.[21,23]

Table 3. Substrate Scope of the Catalytic Oxidation[a]

entry	substrate	product	% yield
1		 R = H X = H	92
2		= OCH_3	96
3		= NO_2	96
4		X = H R = Ph	93[e]
5		= CH_3	95[b,f]
6		= cyclopropyl	90[b,d]
7		= ^{i}Pr	(20)[c,e]
8		= ^{t}Bu	0[c,e]
9			98
10			96[b]
11			98[b]
12			94
13			95
14			96[b]
15			(80)
16			(60)
17			(38)
18			(5)[c,e]
19			(1)[c,e]

[a] Conditions: 2 mol % of **8**, 10 mol % of NEt_3, 1,2-dichloroethane solvent, 60 °C, 24 h. [b] 80 °C. [c] 100 °C, dichlorobenzene solvent. [d] 48 h. [e] 72 h. [f] = 1 equivalent NEt_3. Values in parentheses indicate NMR yield.

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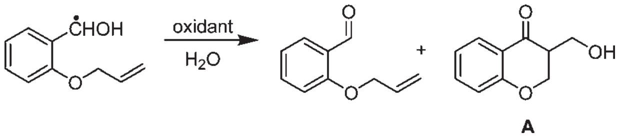
(23) The oxidation of 2-allyloxybenzyl alcohol was also performed on a 10 mmol scale, affording 2-allyloxybenzaldehyde in 94% isolated yield. A minor product identified as 2-allyloxycinnamyl aldehyde was also detected in ca. 2−4% yield; the origin of this product is still under investigation. See the Supporting Information for details.

Scheme 2



The secondary propargylic alcohol 4-phenyl-3-butyn-2-ol was also oxidized in high yield (96%, entry 14). Primary propargylic alcohols 3-phenyl-2-propyn-1-ol and 2-decyn-1-ol were oxidized to the corresponding aldehydes in good yields (80% and 60% ^{1}H NMR yields, entries 15 and 16, respectively). Oxidation of the terminal alkyne 1-phenyl-2-propyn-1-ol was less selective, affording the ketone product in only 38% yield (^{1}H NMR, entry 17) at complete conversion.

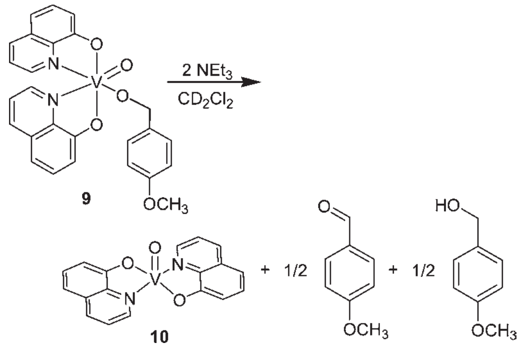
Simple aliphatic alcohols such as 1-butanol and 2-butanol underwent little or no oxidation, even when heated at 100 °C (entries 18 and 19). This observed selectivity for activated alcohols was confirmed by oxidation of a mixture of 4-methoxybenzyl alcohol (5 mmol) and 1-octanol (5 mmol), which resulted in complete oxidation of the benzylic alcohol with no formation of 1-octanal.[20]

For several of the benzylic alcohols, the oxidation proceeded selectively with no solvent (neat) using **8** (2 mol %) and NEt_3 (10 mol %) for 24 h at 100 °C.[20] However, lower selectivities were observed for the oxidations of cinnamyl alcohol, 5-hydroxymethylfurfural, and 4-phenyl-3-butyn-2-ol when no solvent was used.[20]

To gain insight into the role of the base additive, $(HQ)_2V^V(O)(OC_6H_4OCH_3)$ (**9**) was prepared from the reaction of **8** with 4-methoxybenzyl alcohol in acetonitrile. In the absence of base, complex **9** was relatively stable in CD_2Cl_2 solution, with less than 5% reacting after 16 h at room temperature. However, a rapid reaction occurred when a CD_2Cl_2 solution of **9** was treated with NEt_3 (2 equiv) under argon, affording the vanadium(IV) complex $(HQ)_2V^{IV}(O)$ (**10**), 4-methoxybenzaldehyde (0.5 equiv, 100% yield), and 4-methoxybenzyl alcohol (0.5 equiv, 100% yield) within 2 h at room temperature (Scheme 3). The increased reactivity observed in the presence of NEt_3 suggests a key role for the base additive in promoting the alcohol oxidation step. When the reaction of **9** with NEt_3 was carried out under air in CD_2Cl_2, quantitative conversion to the *cis*-dioxo vanadium(V) complex $(HQ)_2V^V(O)_2HNEt_3$ (**11**) and 4-methoxybenzaldehyde was observed after 22 h at room temperature. Complex **11** was independently prepared by the reaction of the μ-oxo complex $[(HQ)_2V^V(O)]_2\mu$-O (**12**)[18a] with H_2O and NEt_3 in CH_2Cl_2. When tested for the oxidation of 4-methoxybenzyl alcohol in combination with 10 mol % of NEt_3, both complexes **10** and **11** were effective catalysts, affording complete conversion in 24 h at 60 °C.

Initial experiments suggest that mass transport of oxygen may be a rate-limiting factor in the oxidation of

Scheme 3



4-methoxybenzyl alcohol.[24] When the oxidation was carried out in two different reaction vessels under otherwise identical conditions and stopped at an intermediate reaction time (4 h),[25] the shape of the reaction vessel affected the extent of conversion. In a wide 100 mL round-bottom flask, 55% conversion was observed after 4 h, while in a narrow 10 mL reaction tube, only 31% conversion occurred. The stir rate also affected the extent of conversion in two identical reactions conducted in 25 mL round-bottom flasks.[20]

In 1,2-dichloroethane, the catalytic oxidation of 4-methoxybenzyl alcohol was not found to be significantly affected by added water. When excess water (5 equiv, 5 mmol) was added to the oxidation of 4-methoxybenzyl alcohol (1 mmol), $>98\%$ conversion to the aldehyde was observed after 24 h at 60 °C. This tolerance of water allows the catalytic reaction to be carried out in the absence of drying agent, in contrast to several other reported vanadium catalysts which require the addition of molecular sieves.[7,12]

In conclusion, the 8-quinolinate vanadium complex **8** catalyzes the oxidation of benzylic, allylic, and propargylic alcohols using air. A base promoter is required for the catalytic oxidation, with very low yield observed in the absence of any basic additives. The catalyst can be prepared in one step under air using commercially available reagents, making the overall process easy, versatile, and mild. Mechanistic studies of the catalytic reaction and efforts to develop more effective catalysts for aliphatic alcohols are currently underway.

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Supporting Information Available. Experimental procedures, synthesis and characterization of vanadium complexes, and NMR spectra of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348–4355.

(25) Conditions: 2 mol % of **8**, 10 mol % of NEt_3, 1,2-dichloroethane solvent, 60 °C.