Chemoselective Aerobic Oxidation of Alcohols Utilizing a Vanadium(V) Catalyst.

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KEYWORDS: vanadium catalysis, chemoselective oxidations, aerobic oxidation, diols.

ABSTRACT: Work remains to develop an aerobic catalyst that will selectivity oxidize secondary alcohols in the presence of primary alcohols. In principle, it is possible when there is an oxidation potential preference for doing so. One potential strategy is the use of a low oxidation potential catalyst. Recently, we reported a dimeric vanadium(V)- (μ-O)$_2$ perfluoropinacolate (pin^F) complex with the ability to oxidize alcohols via dehydrogenation that was sensitive to the alcohol redox potential. Herein, we report the scope, chemoselectivity, and insights into the mechanism by which **V(V) cat** performs oxidations on activated primary and secondary alcohols.

Introduction:

The oxidation of alcohols to aldehydes, ketones, and carboxylic acids are some of the most widely utilized chemical transformations in organic synthesis.[1,2] With its use in chemical feedstock oxidation, active pharmaceutical ingredient (API) preparation, and across academic and industrial synthetic efforts, this foundational reaction requires efficiency, safety, and selectivity, tailored for any given application. Chromium mediated oxidations, such as the Jones oxidation, have broad applicability but have a risk of over-oxidation and use stoichiometric chromium, which is carcinogenic and an acute toxin.[1–4] In contrast, hypervalent iodine (DMP, IBX) and activated DMSO (Swern) oxidations are more selective. However, DMP and IBX are explosive and utilize expensive reagents with relatively short shelf lives[5,6] and Swern oxidations generate dimethyl sulfide, a foul-smelling by-product.[7–9]

Recently, growing interest in developing catalytic aerobic oxidations wherein O_2 is the stoichiometric oxidant has shifted focus towards Pd- and Cu-centered catalysts (**Figure 1A**).[10–13] Palladium has a rich history of redox chemistry, though a number of challenges and limitations exist for the oxidation of alcohols.[14] For example, palladium's propensity to undergo ligation by heterocycles and other Lewis bases, and cross-reactivity with alkene-bearing substrates results in undesired side products.[15] Alternatively, Cu-centered aerobic alcohol oxidations, first demonstrated by Semmelhack,[16] are significantly more tolerant of functional groups, as shown in later systems developed by Markó[17,18] and Sheldon.[19] The similarities of these independently developed systems suggested the potential of a broadly applicable oxidation protocol.

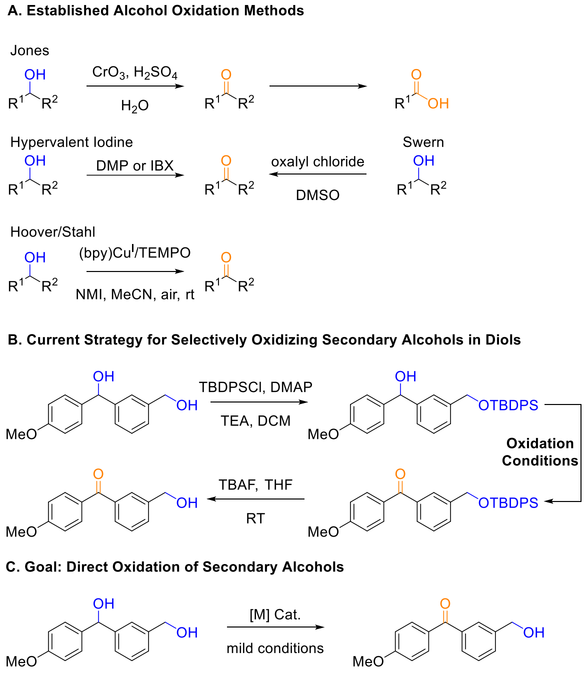


Figure 1: Summary of current alcohol oxidation methods (A) and strategies to selectively oxidize secondary alcohols, in the presence of primary alcohols, utilizing these methods (B). The goal is to present a new method of oxidation that does not require protecting group manipulations to selectively oxidize secondary alcohols in the presence of primary alcohols (C).

The seminal advances in the Hoover-Stahl modifications employing Cu(I) bipyridyl (bpy) complex with N-methylimidazole (NMI) as the base and TEMPO co-catalyst resulted in a wide substrate scope, although phenols and other vicinal Lewis basic groups inhibited reactivity.[10,20] When the Cu/TEMPO conditions were applied to unprotected diols, the catalyst exhibited strong selectivity for the oxidation of primary alcohols, in all cases.[10] Steves and Stahl modified the Hoover-Stahl system, by replacing TEMPO with a less sterically hindered nitroxyl radical, ABNO, to enable oxidation of secondary alcohols.[2,21] Use of the more reactive nitroxyl radical, ABNO, also alleviated issues presented when oxidizing molecules containing vicinal Lewis basic functionalities seen with the oxidations using TEMPO.

Although these two Cu(I)-based systems allow access to a range of aldehydes and ketones, work remains in aerobic oxidative catalysis development, particularly in the development of selective oxidation of secondary alcohols in the presence of primary alcohols (**Figure 1B**). To do so, an alternative strategy to the nitroxyl radical based oxidations developed by Semmelhack, Sheldon, and Stahl, for aerobic oxidation must be employed as these systems have a demonstrated preference for oxidizing the most sterically accessible alcohol.[22]

Vanadium catalysis provides a rich history of both hetero- and homogeneous catalysts for dehydrogenation chemistry. Heterogeneous vanadium catalysts, such as vanadium oxide and V_2O_5/TiO_2, have been utilized in industrial applications to oxidize SO_2 to sulfuric acid,[23] alkylpyridines to nicotinic acid and its derivatives, and methanol to formaldehyde and water.[24] Supported vanadium catalysts are often synthesized via synthetic methodologies that give rise to mixtures of monomeric, dimeric, and polymeric VO_x species on the surface, creating challenges in their characterization and reproducibility.[25] Vanadium is more naturally abundant than copper or palladium, making it an attractive redox metal. Punniyamurthy[26] reports a polyaniline supported $VO(acac)_2$ catalyst that oxidizes benzylic, allylic, and aliphatic primary and secondary alcohols, while Dhakshinamoorthy[27] reports V_2O_5/GO nanocomposites that oxidize benzyl alcohols to their benzaldehydes. Uemura[28] reports calcium phosphate-vanadate apatite (CPVAP) heterogenous catalysis that selectively oxidizes propargylic alcohols to their ynones. Bania[29] demonstrates a unique photo-aerobic oxidation with vanadium oxide supported gold nanocatalysts and Whitehead[30] reports a $Cs_5(V_{14}As_8O_{42}Cl)$ catalyst impregnated on celite that oxidize benzylic, allylic, and aliphatic secondary alcohols. Whitehead also notes primary benzylic alcohols over-oxidize to carboxylic acids. None of the above authors report any selectivity for primary vs secondary alcohols. The above heterogenous vanadium catalysts often require specialized equipment to synthesize, the syntheses take numerous days, the catalyst loadings for reactions are high, and the reaction temperatures often exceed the boiling point of the solvent, requiring an autoclave.

Homogeneous catalysis can be divided into two categories: catalysis via two-electron chemistry or one-electron pathways. Uemera,[31] Toste,[32] and Chen[33] all report proposed vanadium(III) intermediates in their catalytic cycles, resulting from β-hydrogen elimination from an alkoxide ligand. Hanson[34–36] also reported vanadium(III) intermediates via base assisted deprotonation to elicit the dehydrogenation step. In contrast, one-electron pathways involving vanadium(IV) intermediates resulting from hydrogen atom abstraction during alcohol oxidation have been proposed by Ohde and Limberg[37]. The homogenous vanadium systems described were not chemoselective for primary vs secondary alcohol oxidation although many were substrate specific, creating catalyst systems with limited substrates scopes. For example, Uemura[31] reports a method to oxidize propargyl alcohols to ynones. Toste[32] and Chen[33] report oxidative kinetic resolutions of α-hydroxy esters. Baker and Hanson[34] depolymerize lignan species via oxidative C-C bond cleavage reactions. Hanson[35,36] later developed oxidation chemistry of benzylic, allylic, and propargylic alcohols with no radical rearrangements or observed selectivity for primary vs secondary alcohols. Limberg and Ohde[37] observed aerobic oxidation of cinnamic, crotyl, and hydroxyfluorene alcohols with their vanadium complexes. None of the above authors report selectivity for the oxidation of secondary alcohols.

We reported a homogeneous dimeric vanadium(V)- (μ-O)$_2$ perfluoropinacolate, (pin^F) complex (**V(V) cat**, **Figure 2**) that was shown to oxidize alcohols via dehydrogenation and was sensitive to the alcohol redox potential. Herein, we report the scope, selectivity, and insights into the mechanism by which **V(V) cat** performs oxidations on activated primary and secondary alcohols.

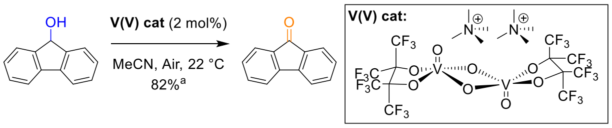


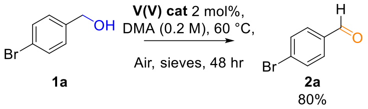
Figure 2: Previously reported oxidation of 9-fluorenol to fluorenone by V(V) cat[38]

Results and Discussion:

Optimization of the oxidation of primary and secondary alcohols to aldehydes and ketones by **V(V) cat** began with a solvent screen (Table S1), which revealed that polar aprotic solvents, such as MeCN and DMA, were the most favorable. Polar protic solvents, such as methanol, promoted catalyst monomerization which was observed by changes in ^{19}F NMR spectra (see section 8 in SI). Ultimately, we found that **V(V) cat** performed best in amide-type solvents such as dimethylacetamide (DMA).

To examine the effect of substrate concentration, catalyst loading, temperature, and the presence of additives, *p*-bromobenzyl alcohol (**1a**) was used as a model substrate. After extensive optimization efforts at a 0.200 mmol scale (**Table 1**, Table S2 for full list of conditions), the optimal reaction concentration was found to be 0.2 M in DMA, with a catalyst loading of 2 mol%, at 60 °C, open to air to allow for the diffusion of oxygen, for 48 hours. It is important to note that at higher reaction concentrations (0.4 M and 0.8 M) and higher catalyst loadings (10 mol%) the reaction mixture turns from yellow to purple, indicating the presence of an unidentified vanadium(IV) species.[38] Higher temperatures can be utilized to accelerate the reaction as evidenced by the shorter reaction time at 80 °C with nearly the same yield.

Table 1: Reaction Optimization Monitoring *p*-bromobenzyl Alcohol to *p*-bromobenzaldehyde



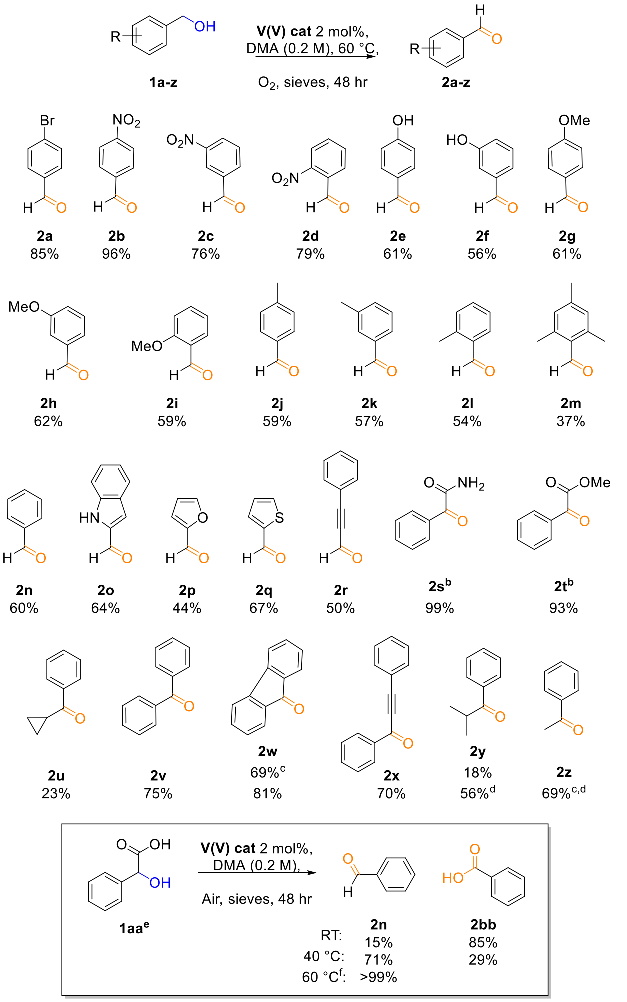
Entry	Variable of Interest	Deviation from Optimized Conditions	Yield of 2a[a]
1	concentration (M)	0.1	61%
2		0.8	67%
3	Catalyst loading (mol%)	0	0%
4		1	68%
5		5	59%
6		10	52%
7	Temperature (°C)	23	4%
8		40	24%
9		80[b]	82%
10	desiccant	No sieves	71%
11		1 wt eq 4 Å powder sieves	64%
12		3 eq water	55%
13	Introduction of air	Oxygen	63%
14		Argon	15%

[a]Quantitative ^{1}H NMR yield determined with 1,3,5-trimethoxybenzene as an internal standard. [b]24 h reaction time.

Considering that 48 hours is a relatively long reaction time, additives were tested to accelerate the reaction or proceed at temperatures lower than 60 – 80 °C. We first introduced nitroxyl radical co-catalysts, TEMPO and ABNO, but with no effect. We also noted no nitroxyl radical adducts, suggesting the lack of discrete radical formation throughout the reaction. To assist with a potential deprotonation, we screened a range of bases from pyridine (pKa = 3.4 in DMSO) to NaOAc (pKa = 12.3 in DMSO) which led to a decrease in yield (46% and 30%, respectively). Addition of extra perfluoropinacolate ligand resulted in a less efficient oxidation, leading to a decreased yield of 38% of **2a** compared to 80% with no additive. Lastly, addition of HFIP, TFE, and PFP had negligible effects on the yield.

Utilizing the optimized conditions, a variety of benzyl alcohols and related activated alcohols were readily oxidized (**Scheme 1**), though cyclohexylmethanol was unreactive. These substrates were scaled to 1 mmol, which required the use of desiccants and a pure O_2 atmosphere (Table S5 for 1 mmol reaction studies). The reaction tolerates both electron donating groups (OMe) and electron withdrawing groups (NO_2). In general, substrates with electron withdrawing groups led to higher yields (**2a**-**2d**), while electron neutral substrates and those with electron donating groups have similar yields (**2e-2l**, **2n**). Another trend that emerges when analyzing *o*-, *m*-, and *p*-substituted methoxy benzyl alcohols is that each is oxidized to its respective aldehyde (**2g-2i**) in approximately the same yield (59 to 61%) despite the differences in sterics and electronics.

Scheme 1: Primary and secondary activated alcohol scope[a]



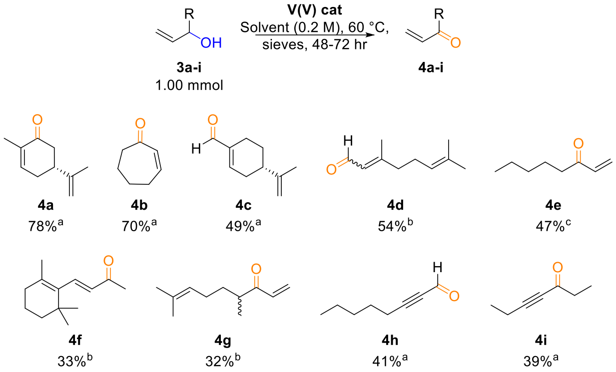
[a]Reaction conditions: Alcohol substrate (1.00 mmol), **V(V) cat** (0.02 mmol, 2 mol%), DMA (0.2 M), 60 °C, Oxygen, 1 wt. eq. of 4Å bead sieves, 48 hr. Quantitative ^{1}H NMR yield determined with 1,3,5-trimethoxybenzene as an internal standard. [b]RT. [c]24 hours. [d]80 °C. [e]Reaction conditions: mandelic acid (0.200 mmol), **V(V) cat** (0.02 mmol, 2 mol%), DMA (0.2 M), Air, 1 wt. eq. of 4Å bead sieves, 48 hr at the stated temperature. Monitored by NMR conversion. [f]Control experiment: mandelic acid (0.200 mmol), DMA (0.2 M), Air, 1 wt. eq. of 4Å bead sieves, 48 hr, 60 °C; no reaction occurred.

These substrates have similar oxidation potentials (1.3 V, 1.4 V, and 1.3 V, respectively) which may explain their similarities in reactivity.[39] *o*-hydroxybenzyl alcohol did not oxidize to its corresponding aldehyde. Instead, the reaction changed color from yellow to purple, strongly suggesting the formation of an unknown vanadium (IV) species. More hindered substrates, such as mesityl benzyl alcohol **1m,** gave lower yields presumably due to their difficulty approaching the vanadium center. Increasing the temperature to 80 °C for 24 hours overcame the steric barrier to a limited extent, and **1m** produced **2m** in a 41% yield.

Secondary benzyl alcohols **1s** – **1z** (**Scheme 1**) were also cleanly oxidized, although in somewhat lesser yields, as seen with **1u** and **1y**. Under the optimized conditions, the cyclopropyl group found in product **2u** remained intact, with the only other molecule present in the ^{1}H NMR being the starting material **1u**. Secondary alcohols **1v** and **1w** have lower oxidation potentials due to the presence of the second aromatic substituent, resulting in significantly higher yields (75% and 81%, respectively). Additionally, mandelic acid **1aa** (**Scheme 1**) was anticipated to cleanly oxidize to phenylglyoxylic acid, in a similar manner as mandelamide (**1s**) and methyl mandelate (**1t**). Instead, C-C bond cleavage resulted in the release of CO_2, producing benzaldehyde (**2n**), and depending on the temperature, benzoic acid (**2bb**). When mandelic acid **1aa** was exposed to **V(V) cat** at 60 °C, we saw a 99% conversion to benzaldehyde **2n**. Interestingly, when the temperature was lowered to 40 °C, we observed the appearance of benzoic acid **2bb** (29%) and at room temperature, the conversion increased to 85%. We attribute this observed reactivity to O_2's increased retention in DMA at room temperature[40,41], facilitating auto-oxidation of benzaldehyde.[42,43]

Next, **V(V) cat** was applied to the oxidation of allylic alcohols **3a-g** to yield oxidation products **4a-g** and propargylic alcohols **3h-3i** to yield **4h-4i** (**Scheme 2**). Substrates **3a-c** and **3h-3i** readily oxidize utilizing the previously established conditions with good to moderate yields and no ^{1}H NMR detectable byproducts, such as epoxides or allenes, respectively. In contrast, substrates **3d-3g**, which are not constrained as cyclic alcohols, were unsuccessful with the optimized conditions in DMA, affording epoxide side-products. To overcome this, the solvent was changed to MeCN, and the amount of catalyst was increased from 2 mol% to 4 mol%. Using these conditions, allylic alcohols were cleanly oxidized in good to moderate yields.

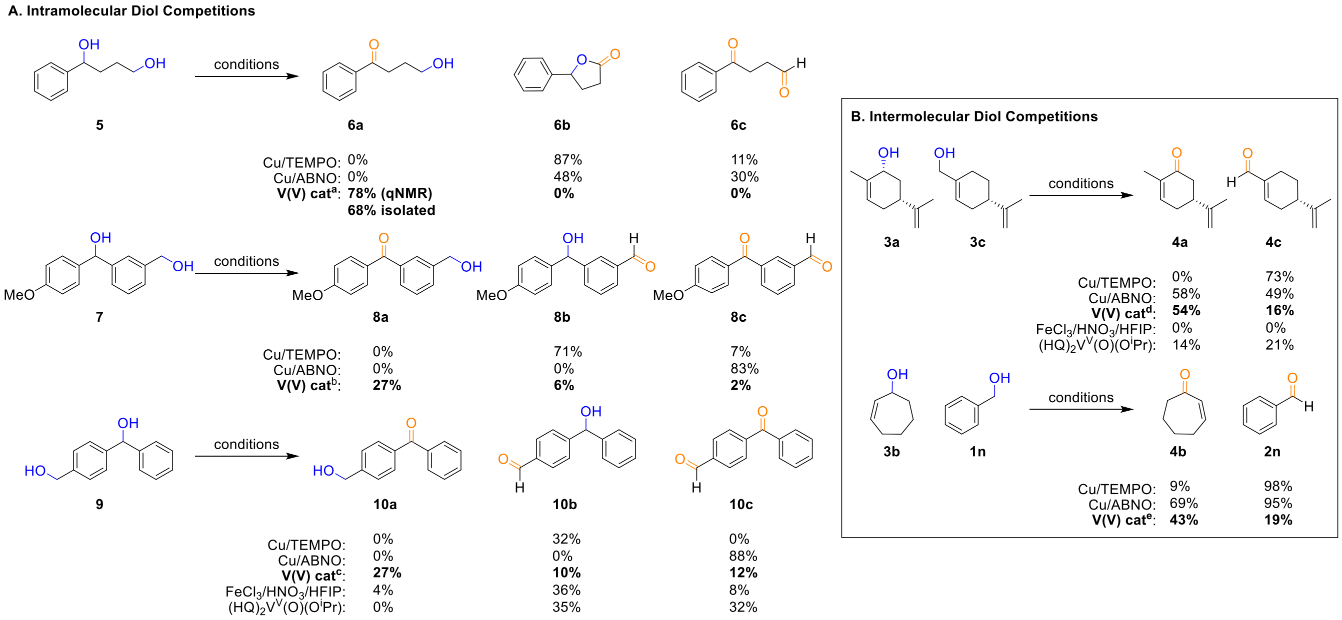
Scheme 2: Allylic and Propargylic Alcohol Scope



[a]Reaction conditions: **V(V) cat** (0.02 mmol, 2 mol%), DMA (0.2 M), O_2, 1 wt. eq. of 4Å bead sieves, 48 hr. Quantitative ^{1}H NMR yield determined with 1,3,5-trimethoxybenzene as an internal standard. [b]Reaction conditions: **V(V) cat** (0.04 mmol, 4 mol%), MeCN (0.2 M), Air, 1 wt. eq. of 4Å bead sieves, 72 hr. Quantitative ^{1}H NMR yield determined with 1,3,5-trimethoxybenzene as an internal standard. [c]Reaction conditions (a), but in MeCN.

The above data suggest that activated primary and secondary alcohols can be oxidized with ease utilizing **V(V) cat** and potentially provides an opportunity for selective oxidation of activated secondary alcohols in the presence of primary alcohols. To test this possibility, several intra- and intermolecular chemoselectivity competitions were designed.

Scheme 3: Chemoselectivity Studies on Diol Substrates



[a]Reaction conditions: **V(V) cat** (0.02 mmol, 2 mol%), DMA (0.2 M), O_2, 80 °C, 48 hr. Isolated Yields. [b]Reaction conditions: **V(V) cat** (0.05 mmol, 5 mol%), MeCN (0.25 M), Air, 22 °C, 72 hr. Isolated Yields. [c]Reaction conditions: **V(V) cat** (0.01 mmol, 1 mol%), MeCN (0.2 M), Air, 40 °C, 72 hr. Isolated Yields. [d]Reaction conditions: **V(V) cat** (0.04 mmol, 4 mol%), MeCN (0.1 M), Air, 40 °C, 72 hr. Isolated Yields. [e]Reaction conditions: **V(V) cat** (0.01 mmol, 1 mol%), MeCN (0.25 M), Air, 40 °C, 72 hr. Quantitative ^{1}H NMR yield determined with 1,3,5-trimethoxybenzene as an internal standard.

Each unprotected diol (**5**, **7**, **9**, **Scheme 3A**) and intermolecular competition (**3a**/**3c** and **3b**/**1n**, **Scheme 3B**) was subjected to Hoover/Stahl, Steves/Stahl, and **V(V) cat** oxidation conditions to demonstrate selectivity (additional selectivity studies[35,44] for diols **9** and **3a**/**3c**). The anticipated selectivity of **V(V) cat** for less sterically accessible alcohols would make it invaluable in total synthesis efforts where step count minimization and eliminating the use of protecting groups afford the most expeditious synthetic route.

To establish a baseline for reactivity and to validate observations made by Stahl, diol **5** was subjected to Cu/TEMPO and Cu/ABNO oxidations as described in literature.[2,10] Expectedly, Stahl's Cu/TEMPO oxidation strongly favored oxidation of the primary alcohol and subsequent formation of the lactone (8:1 ratio). Cu/ABNO demonstrated general oxidation of diol **5** with no selectivity (1.6:1 **6b**:**6c**). Gratifyingly, **V(V) cat** exhibited complete selectivity for the oxidation of the secondary benzyl alcohol (**6a**) over the sterically more accessible aliphatic primary alcohol.

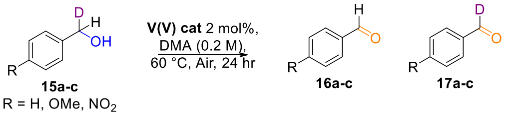
Diols **7** and **9** were evaluated to further explore potential chemoselectivity (**Scheme 3A**). Stahl's Cu/TEMPO oxidation strongly favored oxidation of the primary alcohol over the secondary (~10:1 for **7**, but only 32% yield for primary alcohol oxidation of **9**) (**Scheme 3A**). Moreover, Stahl's Cu/ABNO oxidation system showed complete selectivity for globally bis-oxidized products **8c** and **10c**. Oxidation with $FeCl_3/HNO_3$/HFIP[44] resulted in 9:1 selectivity for **10b** over **10a**, while $(HQ)_2V^V(O)(O^iPr)$[35] provided a 1:1 mixture of **10b** and **10c**. Most rewardingly, treatment of diols **7** and **9** with **V(V) cat** in MeCN resulted in selectivity favoring the secondary alcohol over the more accessible primary alcohol by 4.5:1 and 2.7:1 ratio, respectively. Notably, only **V(V) cat** provided direct access to the mono-oxidized benzophenone from diols **7** and **9** in appreciable yields. We also carried out intermolecular competition studies using allylic alcohols **3a**/**3c** and **V(V) cat** maintained selectivity for activated secondary alcohols over primary alcohols in a 3.3:1 ratio (**Scheme 3B**). Oxidation with Cu/TEMPO selectively produced perillaldehyde (**4c**) and Cu/ABNO oxidized both allylic alcohols (~1.2:1 ratio). Oxidation with $FeCl_3/HNO_3$/HFIP[44] resulted in complete degradation of the starting alcohols, while $(HQ)_2V^V(O)(O^iPr)$[35] provided a 1:1.5 mixture of **4a** and **4c**. Another intermolecular competition study between **3b**/**1n** (**Scheme 3B**) revealed a preference for the oxidation of cyclic secondary allylic alcohols over primary benzyl alcohols in a 2.3:1 ratio.

Preliminary Mechanistic Studies:

Compared to benzyl alcohol, both *p*-methoxy and *p*-nitro derivatives showed higher conversion in DMA (**Figure 3A**), while the conversions of all three alcohols were comparable in MeCN. Since these results do not follow a standard Hammett relationship, kinetic isotope effect studies were done, using the monodeutero derivatives, to better understand the rate limiting step. The resulting k_H/k_D ratios were approximately 7 in DMA but varied based upon the electronics of the substrate in MeCN, indicating a primary isotope effect and that the rate limiting step was the dehydrogenation of the carbinol hydrogen for each substrate.

DFT studies were undertaken to probe the mechanism in more detail, and the current proposal is shown in **Figure 4**. The catalytic cycle begins with benzyl alcohol associating to **V(V) cat** as a ligand (**18**), followed by proton transfer of the hydroxyl -OH to the bridging μ-oxo, resulting in an alkoxide bound to **V(V) cat** (**19**). This species rapidly opens to {V(V)V(V)} **20**, allowing for proposed β-hydrogen elimination—the rate limiting step—to a terminal oxo to form the product aldehyde or ketone, and terminal hydroxide group. This step was calculated in detail for the three substrates used in the deuterium labeling. Both experiment and theory suggest the carbinol proton is equally shared between the terminal oxo of the vanadium catalyst and the carbon of the substrate (**20a** in **Figure 3B**) in the transition state. This net transfer of one proton and two electrons results in one terminal hydroxide, and the reduction of one V(V) to V(III). The organic product is rapidly released from the metal center, with reclosure of the dimer and intramolecular electron transfer, to form **22** with two V(IV) centers and two μ_2-OH ligands (synthesis, reactivity, and crystal structure previously reported[38]). Aerobic re-oxidation by ambient O_2 forms structure **23**, which expels hydrogen peroxide to reform **V(V) cat** to continue the cycle.

A. Kinetic Isotope Effects



A. DMA

R^a	Conversion (16 + 17)	k_H/k_D
H	33%	6.8
OMe	44%	7.1
NO_2	76%	7.0

B. MeCN

R^b	Conversion (16 + 17)	k_H/k_D
H	32%	4.6
OMe	34%	6.8
NO_2	42%	5.4

B. Qualitative Energy Calculations of Transition States

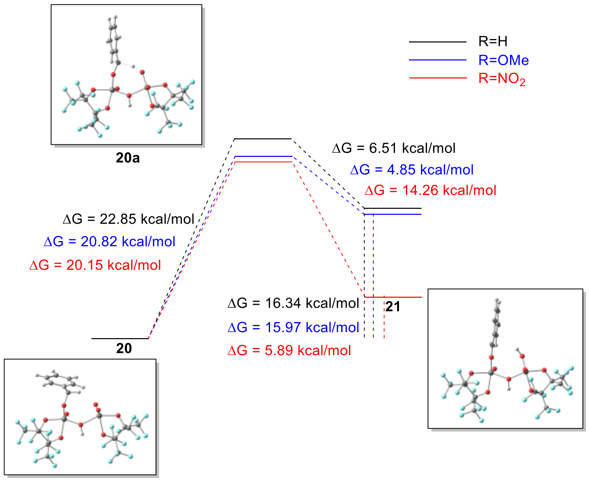


Figure 3: (A) Substrates for kinetic isotope effect studies and proposed mechanism. [a]Two runs of *p*-OMe and *p*-NO_2 each, one of H. [b]Two runs of each substrate. (B) DFT calculations support carbinol proton transfer from benzyl alkoxide ligand to a {V(V)V(V)} vanadium dimer in the open state.

A persistent radical process was not favored since the oxidation of **1u** did not result in any cyclopropyl ring opening (**Scheme 1**), and the addition of TEMPO did not have an impact on the oxidation of **1a**. Preliminary DFT calculations further support the lack of a radical in the mechanism, as the transfer of the second hydrogen atom to a terminal oxo via β-hydrogen elimination has an energy barrier of $\Delta G = 22.85$ for benzyl alcohol (**Figure 3B**). Furthermore, the calculations suggest the barrier to transfer the carbinol proton is lower in *p*-OMe and *p*-NO_2 benzyl alcohols, which agrees with the experimental results seen in **Figure 3A**.

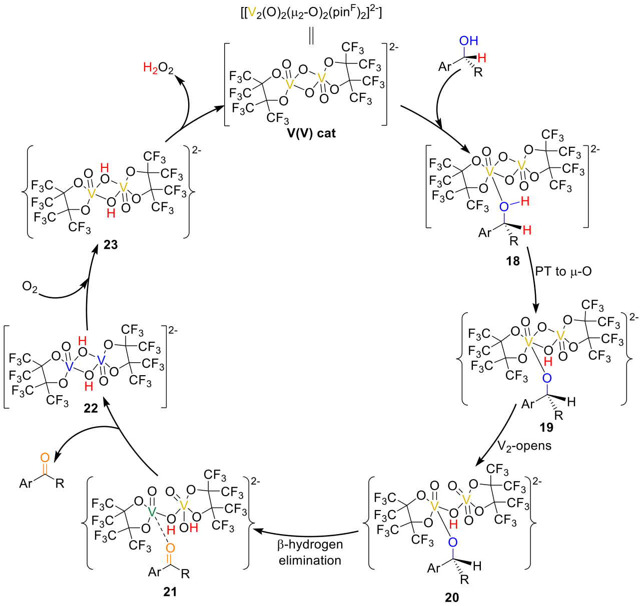


Figure 4: Proposed catalytic cycle for the oxidation of benzyl alcohols by **V(V) cat**.

Conclusions

The **V(V) catalyst** may offer a practical, chemoselective oxidation protocol complementary to existing aerobic oxidations. This reaction expands the current repertoire of selective oxidations of unprotected diols and polyols, a valuable advancement in synthetic organic chemistry by decreasing reliance on protecting group strategies. This advance would reduce step count, thereby drastically improving atom economy in the synthesis of complex organic molecules. Furthermore, the catalyst is easy to prepare and bench stable under ambient conditions for several years.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge at http://pubs.acs.org

Synthesis and characterization (PDF)

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Funding Sources

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The authors thank Dr. Norman Lee (Boston University) for HRMS data and analyses. We thank Dr. Paul Ralifo (Boston University) for assistance with in-situ qNMR acquisition. We also thank the National Science Foundation (NSF) for support of NMR (CHE-0619330) and MS (CHE-0443618) facilities at Boston University and support for this work (CHE CAT 0212532 to L.H.D.). Computational work reported in this paper was performed on the Shared Computing Cluster (SCC), which is administered by Boston University's Research Computing Services.

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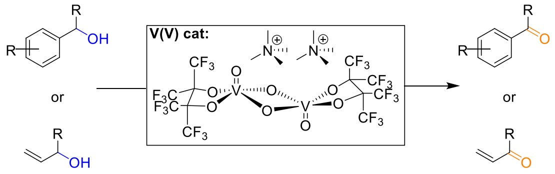

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