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Tuning the oxidation properties of vanadium(V) through ligand stoichiometry

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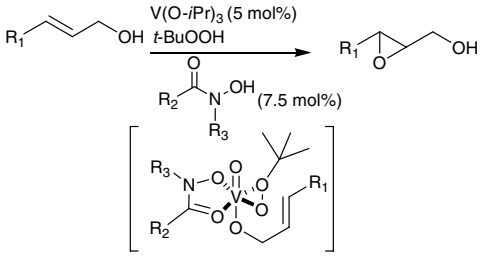
Abstract—Vanadium(V) (5 mol %) and hydroxamic acid ligand (45 mol %) were found to promote the selective *tert*-butyl hydroperoxide-mediated oxidation of allylic and propargylic alcohols to the corresponding aldehydes and ketones.

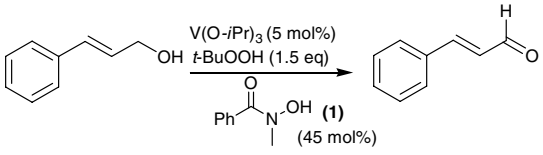
As an oxidation catalyst, vanadium mediates a wide array of synthetic transformations, including the epoxidation of allylic alcohols, and the oxidation of activated C–H bonds, sulfides, and primary/secondary alcohols.[1] In each of these aforementioned cases, the scope of the synthetic transformation (i.e., epoxidation vs oxidation) has been dictated by the reaction conditions and substrate identity. In this letter, we report an alternative approach to controlling the reactivity of a vanadium-based catalyst system through varying ligand stoichiometry.

Allylic alcohols have been employed for decades as model substrates for the investigation of novel epoxidation catalysts. In this regard, a number of reports have documented that vanadium(V), in combination with a hydroxamic acid (HA) ligand (5.0 mol % metal and 7.5–15 mol % ligand) and *tert*-butyl hydroperoxide (TBHP) will selectively catalyze the epoxidation of a wide range of allylic alcohols into their corresponding epoxy alcohols via the proposed peroxovanadium intermediate[2] depicted below (Scheme 1).[3] We have discovered that by increasing the stoichiometry of the HA ligand, the course of this oxidation reaction can be fundamentally altered to produce metal complexes that no longer perform epoxidation reactions but that selectively oxidize[4] allylic and propargylic alcohols to the corresponding aldehydes and ketones with moderate yields under mild conditions with a minimal quantity of the metal catalyst.



Scheme 1.

Optimal conditions for this transformation were first determined by studying the conversion of cinnamyl alcohol to cinnamyl aldehyde (Scheme 2). The yield of the reaction was maximized by systematically investigating the ligand/metal ratio, reaction solvent, reaction time, reaction temperature, oxidant concentration, and catalyst/substrate ratio. We found that we could achieve a 50% yield of cinnamyl aldehyde from cinnamyl alcohol at room temperature in toluene by using 5 mol % $VO(O\text{-}iPr)_3$, 45 mol % *N*-hydroxy-*N*-methylbenzamide **1**,[5] and 150 mol % (1.5 equiv) of TBHP. In addition, we observed that if the HA ligand, the TBHP, or the vanadium(V) were omitted, no reaction occurred.



Scheme 2.

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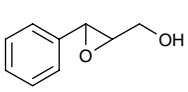
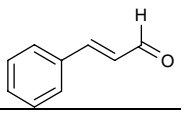
Table 1. The effect of ligand/metal ratio on vanadium-mediated oxidation of cinnamyl alcohol[a]

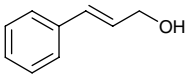
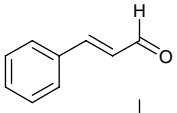
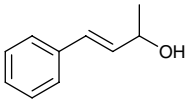
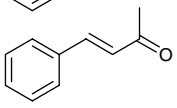
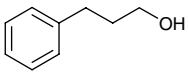
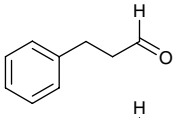
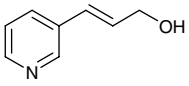
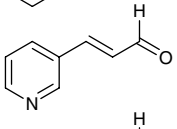
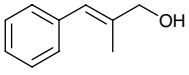
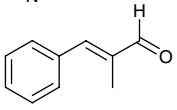
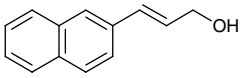
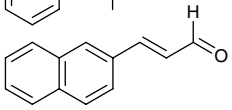
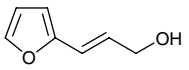
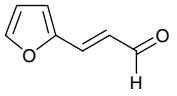
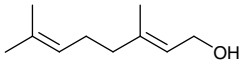
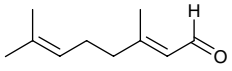
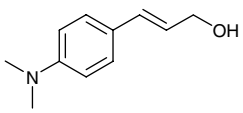
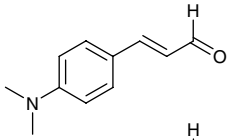
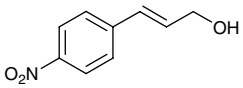
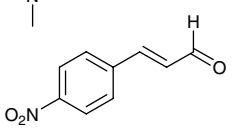
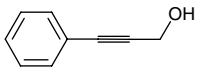
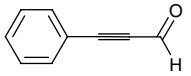
Entry	Ligand/metal ratio (mol/mol)	Yield[b] (%)	
			
1	1.5	0	65 (70)[c]
2	3.0	9	32
3	4.0	18	21
4	5.0	24	13
5	7.0	32	<5
6	9.0	50	0
7	11	31	0

[a] Procedure identical to outlined in Ref. 9, only ligand concentration was varied.
[b] Isolated yield after column chromatography.
[c] Yield in parenthesis is the previously reported yield.[3c]

From these optimization experiments, we also determined the extent to which the ligand-to-metal ratio (LMR) controlled the reactivity of this system. This data is summarized in Table 1. At 7.5 mol % vanadium(V) and 11.3 mol % HA ligand **1** (LMR = 1.5), we achieved 65% conversion to the epoxy alcohol (similar to the 70% yield that was previously reported).[3c] With 7.5% vanadium(V) and 22.5% we observed that the oxidation system started to perform both allylic oxidation and epoxidation reactions. The ratio of oxidation/epoxidation product increased until the LMR reached 9, at which point only oxidation was observable.

Next, the substrate scope of the reaction was established by studying the oxidation of various primary and secondary alcohols to their corresponding aldehydes and ketones. As can be seen from Table 2, this reagent combination selectively oxidizes allylic and propargylic alco-

Table 2. Catalytic oxidation of primary and secondary alcohols in the presence of vanadium/hydroxamic acid complex[9]

Entry	Substrate	Time (h)	Product	Yield[a] (%)
1		48		50
2		72		28
3		48		0
4		24		46
5		48		44
6		48		41
7		48		22
8		48		28
9		24		14
10		48		66
11		72		67

[a] Isolated yield after column chromatography.

hols to their corresponding aldehydes and ketones. No epoxy alcohol could be detected under these reaction conditions. We have compared the reactivity of primary and secondary allylic alcohols (entries 1 and 2), and have discovered that the primary alcohol is oxidized to the corresponding aldehyde in higher yield in a shorter time frame than the secondary alcohol (50% yield in 48 h vs 28% yield in 72 h). The vanadium/hydroxamic acid complex does not oxidize primary alcohols that are not allylic/propargylic (entry 3), and is tolerant to pyridine functionality (entry 4). Propargylic substrates (entry 11) or substrates with a conjugated electron withdrawing substituent (entry 10) were oxidized in the highest yield. Analysis of the efficiency in which our substrates are oxidized indicates that both steric and electronic effects govern the oxidation system. Increasing the steric hindrance of the allylic alcohol at C_α leads to a substantial decrease in product yield (entries 1 and 2), while decreasing the steric hindrance of the substrate at C_α leads to improved oxidation yield (entries 1 and 11). Electronic effects also play a key role in this catalyst sytem, as increasing the electron density of the allylic double bond leads to decreased product yield, while electron deficient substrates enhance oxidation performance (entries 1, 9, and 10).

Based upon early observations that epoxidation is inhibited by excess HA ligand,[6] the elevated concentration of the hydroxamic acid ligand most likely forces the vanadium to accommodate an additional HA ligand, leaving only one site available for coordination (vs two coordination sites for the epoxidation catalyst) (Fig. 1). Vanadium-based oxidations of alcohols to their corresponding carbonyl derivatives typically proceed via a $1e^-$ process,[7] so a possible mechanism for this reaction is outlined in Scheme 3. Initially, the HA ligands displace the isopropoxide ligands to form complexes of type **2**. Given the well documented weak affinity of TBHP for vanadium(V) complexes,[8] we propose that the subsequent coordination occurs via addition of the allylic alcohol to complex **2** with concomitant displacement of the final isopropoxide ligand to provide the active complex **3**. Oxidation of the substrate mediated by *tert*-butyl hydroperoxide via a $1e^-$ process generates the desired aldehyde and regenerates the catalyst for further oxidation cycles. However, further mechanistic studies are necessary to validate the proposed catalyst cycle.

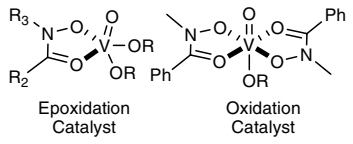
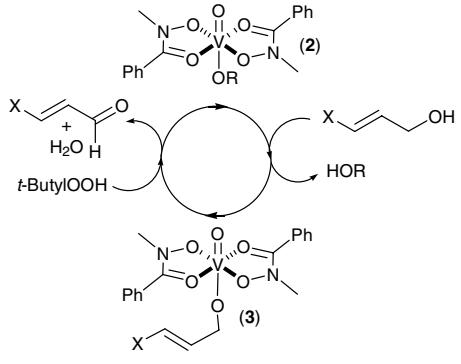


Figure 1.



Scheme 3.

In conclusion, we have shown that the course of a vanadium-based oxidation reaction can be controlled through simple ligand stoichiometry. Since both steric and electronic factors dictate product yield, current efforts are centered on using modified hydroxamic acid ligands to improve reaction yields and substrate scope. We are also exploring the potential of alternative ligands to allow the use of molecular oxygen as the oxidant, and will report our studies in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.051.

References and notes

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9. General experimental procedure for catalytic oxidation: To a solution of the hydroxymate complex of vanadium readily prepared from *N*-hydroxy-*N*-methylbenzamide (50 mg, 0.33 mmol) and $VO(O\text{-}iPr)_3$ (38 μmol, 9 μL) in 6 mL of dry toluene (25 °C, 1 h) were added cinnamyl alcohol (104 mg, 0.776 mmol) and *t*-BuOOH (1.14 mmol, 228 μL, 5.0 M) at −20 °C under an Ar atmosphere. The solution was stirred at −20 to 0 °C for 4 h, the solution allowed to warm to 25 °C and stirred for 48 h. The reaction was distilled to dryness in vacuum, and chromatography of the residue on silica gel gave 51 mg cinnamyl aldehyde (50% yield).