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A Highly Selective Vanadium Catalyst for Benzylic C–H Oxidation

Ji-Bao Xia, Kevin W. Cormier, and Chuo Chen

Division of Chemistry, Department of Biochemistry, The University of Texas Southwestern Medical Center, Dallas, Texas, 75390, USA; Fax: +1 214 6480320; Tel: +1 214 6485048

Chuo Chen: Chuo.Chen@UTSouthwestern.edu

Abstract

Vanadium complexes have been used extensively to catalyze olefin and alcohol oxidation. However, their application in C–H oxidation has not been well-studied. We report herein that commercially available Cp_2VCl_2 catalyzes benzylic C–H oxidation selectively and effectively, giving no aromatic oxidation products.

Introduction

Application of transition metal-catalyzed C–H oxidation to organic synthesis has received increasing attention in recent years.¹ This area of research has been significantly influenced by studies of the C–H oxidizing metalloenzymes. Although many biomimetic^{2–5} and non-biomimetic^{6–14} methods have been reported, selective and efficient C–H oxidation is still difficult to achieve. In addition, the turnover numbers of C–H oxidation catalysts are usually low due to rapid catalyst deactivation. For example, the seemingly straightforward benzylic oxidation of arylalkanes is often complicated by competitive aromatic oxidations, and good catalyst efficiency is observed with only a few complexes.¹⁵ We report herein an efficient vanadium catalyst for selective benzylic C–H oxidation with no competing aromatic oxidation.

Vanadium-catalyzed C–H oxidation has not been a subject of active research. The previously reported work has focused mainly on oxidative coupling of phenols.¹⁶ Nonetheless, Mimoun found that oxidation of cyclohexane by $(\text{pic})\text{VO}(\text{O}_2)\cdot 2\text{H}_2\text{O}$ gave cyclohexanol and cyclohexanone, and oxidation of toluene gave a mixture of cresols along with a small amount of benzyl alcohol and benzaldehyde.¹⁷ The reactivity and selectivity of this catalyst are reminiscent of those of the commonly used C–H oxidizing iron catalyst $[\text{Fe}(\text{BPMEN})(\text{CH}_3\text{CN})_2][\text{ClO}_4]_2$.^{3c,3e} Shul'pin, Pombeiro and others later reported several other effective vanadium catalyst systems.^{18,19} Mechanistic studies suggest that the free

[†]Electronic Supplementary Information (ESI) available: Experimental procedures, details of the KIE study and characterization data are provided (29 pages) (PDF). See DOI: 10.1039/b000000x/

hydroxyl/alkoxy radical is the active oxidant in many of these C–H oxidation reactions. With modest yields and regioselectivities, the synthetic utility of most reported vanadium catalysts is rather limited.

Research Design

Vanadium complexes are well-known for their ability to transfer an oxygen (in directed epoxidation)²⁰ or halogen atom (by halogenase)²¹ to olefins. Considering the transition states of metal-catalyzed olefin and C–H oxidation (Fig. 1), we believed that vanadium complexes could also be good catalysts for C–H oxidation, even though a vanadium hydroxylase remains elusive.

We sought to develop synthetically useful vanadium catalysts with substrate scopes complementary to those of Mimoun's complex and the prevalent iron catalysts. Our initial focus was on the oxidation of arylalkanes. We aimed to achieve selective benzylic C(sp³)–H oxidation by suppressing aromatic C(sp²)–H oxidation and non-metal-based radical oxidation.

Results and Discussion

We started our study by investigating the oxidative ability of a series of vanadium catalysts. We discovered that VO(acac)₂/TBHP,^{19a} a commonly used catalyst/oxidant combination for directed epoxidation,²⁰ promoted the benzylic oxidation of ethylbenzene selectively and effectively at 30 °C when no solvent was used (Table 1, entry 1). Unlike Mimoun's complex, it did not afford any aromatic oxidation products based on ¹H NMR analysis. A number of other vanadium catalysts were also found to promote benzylic oxidation. For example, VOF₃ and VOCl₃ showed comparable reactivity and selectivity, but VO(O^{*i*}Pr)₃ and V₂O₅ were less effective (entries 2–5). The best results were obtained with vanadocene dichloride (entry 6). Using 1 mol % Cp₂VCl₂ and 5 equiv TBHP, oxidation of ethylbenzene at 30 °C gave acetophenone in 87–90% isolated yield. The only detectable byproducts in the crude reaction mixture by GC and ¹H NMR were 1–2% of benzylic peroxide PhCH(OO^{*i*}Bu)CH₃ and benzaldehyde (see ESI). Significantly lower turnover numbers were observed at higher temperature, indicating that the active catalyst is thermally unstable. Reducing the amount of TBHP or the reaction time also led to a significant decrease of conversion (entries 7–9). While no solvent is required, acetonitrile could be used to dissolve the substrates (entry 10). Among all the oxidants examined, TBHP is the only effective oxidant (entries 11 and 12).²² This reaction can be conducted under argon or ambient atmosphere.

The substrate scope of this benzylic oxidation is shown in Table 2. The 4-position of the phenyl ring can tolerate a variety of substituents (fluoro, chloro, acetyl, cyano, or methoxyl) with different electronic properties (entries 1–6). The desired ketones were all obtained in good yields except for the oxidation of 4-ethylanisole (entry 6). The 3-position is also not sensitive to electronic perturbation (cyano, carboxyl, bromo, or methoxyl). The desired ketone products were all formed in good yields (entries 7–10). However, in the presence of a 2-substituent (chloro or methoxyl), the ketone formation was less efficient (entries 11 and 12). It is noteworthy that, unlike typical electron transfer-type oxidation reactions,^{13b} double oxidation occurred with Cp₂VCl₂/TBHP when two alkyl side-chains were present. Oxidation of 1,4-diethylbenzene with 2 mol % Cp₂VCl₂ and 10 equiv TBHP afforded 86% yield of the diketone (entry 13).

A series of different side-chains has also been found to undergo smooth oxidation with no competing aromatic oxidation. The methyl group of 4-methylbiphenyl was oxidized cleanly to the acid despite lower conversion (entry 14). Extending the length of the side-chain also

reduced the catalyst efficiency (entries 15–18). Oxidation of phenyloctane (entry 15) gave 57% yield of the desired ketone and 13% yield of the recovered starting material. We did not observe any phenolic and alcohol products in the crude ^1H NMR spectra (see ESI). The major byproducts were 9% yield of the benzylic *tert*-butylperoxide and 10% yield of benzoic acid. We also isolated 3%, 1% and 1% yield of the 1,4-, 1,5- and 1,6-diketone as the minor byproducts. The mass balance of these materials is 94%. The diketones were most likely derived from an intramolecular hydrogen abstraction reaction of the benzylic radical, as subjecting the benzylic ketone to the reaction conditions did not give any diketones.

We noted that this new oxidation method can be used as an alternative approach for aldol synthesis. For example, 2-methyl-4-phenyl-2-butanol was oxidized cleanly to afford the corresponding ketone in 50% yield (entry 19). Finally, oxidation of the highly activated diphenylmethane also proceeded uneventfully (entry 20).

The available evidence suggests that this vanadium-catalyzed benzylic oxidation reaction occurred through a C–H abstraction mechanism (Fig. 2). The green Cp_2VCl_2 solution turned orange quickly upon addition of TBHP, indicating a valence change from V(IV) to V(V). Since VOX_3 also catalyzed benzylic oxidation effectively, the reactive species generated from $\text{Cp}_2\text{VCl}_2/\text{TBHP}$ is likely to be **II**, the valence tautomer of **I**.²³ It abstracts a proton to give the benzylic radical and **III**. Subsequent rebound affords the benzylic alcohol, which is further oxidized to ketone. Reaction of **IV** with TBHP regenerates **I/II**.

To prove the intermediacy of a benzylic alcohol, we subjected cumene (**3**) to our standard oxidation conditions (Scheme 1). The predicted benzylic alcohol **4** was indeed isolated in 77% yield. To demonstrate that benzylic alcohols could be oxidized to ketones, we treated alcohol **5** with the standard oxidation conditions and found that ketone **6** could be obtained quantitatively in 1 day. We have also examined the possibility of ketone formation through benzylic peroxide and have found that $\text{PhCH}(\text{OO}^t\text{Bu})\text{C}_7\text{H}_{15}$ was stable to Cp_2VCl_2 or TBHP alone. Treating it with the standard oxidation conditions gave **6** cleanly but only in 30% yield after 6 days. We therefore conclude that ketone **6** was formed predominantly through oxidation of **5** instead of decomposition or oxidation of the benzylic peroxide.

The Fenton reaction has long been suspected to be a competitive reaction in metal-catalyzed C–H oxidation.^{24,25} Non-metal-based free radicals have also been recognized as the reactive species in copper- and palladium-catalyzed allylic oxidation^{2d,9b} and many vanadium-catalyzed C–H oxidation reactions.^{18,19} While it is difficult to unequivocally exclude this possibility, the following observations suggest that our benzylic C–H oxidation reaction is not mediated by $^t\text{BuO}^\bullet$ or $^t\text{BuOO}^\bullet$, the Haber–Weiss decomposition products of TBHP.

First, the rate of our vanadium-catalyzed oxidation reaction is significantly lower than that of the common Fenton reactions. Although it is possible that the low reaction rate is due to a slow generation of free radicals, kinetic isotope effect (KIE) studies show that the C–H cleavage instead of the reactive species generation is the rate limiting step. Second, the Cp_2VCl_2 -catalyzed oxidation reaction did not yield any benzylic hydroperoxide (ROOH), the common Fenton reaction product derived from trapping of the evolved O_2 by the radical intermediates. Third, no reaction occurred when H_2O_2 and NaClO were used as the oxidants. Substituting FeCl_2 or CuCl_2 for Cp_2VCl_2 in an attempt to induce the Fenton oxidation of phenyloctane also gave less than 5% yield of **6**. Fourth, cyclohexane is known to be oxidized by $\text{RO}^\bullet$ or $\text{ROO}^\bullet$ but failed to react under our conditions. Olefins are also relatively inert under these conditions. Fifth, addition of radical inhibitor BHT (2 mol %) in order to suppress the radical initiation had no significant effects on the oxidation of phenyloctane, indicating that the reaction is not a radical chain reaction mediated by $^t\text{BuO}^\bullet$ generated from catalyst activation (for example, $\text{I/II} \rightarrow \text{Cp}_2\text{V}(\text{O})\text{X} + ^t\text{BuO}^\bullet$).²³ Sixth,

addition of radical trap BrCCl_3 (1 equiv) in an attempt to capture this benzylic radical failed, indicating that the rebound of **III** and the benzylic radical is relatively fast and possibly occurs in the solvent cage. This C–H abstraction/rebound may proceed in a nearly concerted asynchronous manner as shown in Fig. 1.

To gain further insights into this reaction, we measured the KIE in the oxidation of cumene (**3**). The heterogeneity of this reaction prevented an accurate time-course kinetic study, and the pseudo-first-order oxidation of **3** could not be established by using excess Cp_2VCl_2 and limited TBHP because Cp_2VCl_2 is a pre-catalyst. We therefore measured the KIE by setting up a competing experiment of **3** and the benzylically deuterated cumene (**3-*d*₁**) under the standard oxidation conditions. The reaction was stopped at low conversion (determined by GC with calibration). Assuming that the catalyst concentration did not change significantly over this period of time, the KIE value was then calculated from the ratio of recovered **3/3-*d*₁** (determined by ^1H NMR). We observed a very strong primary KIE ($k_{\text{H}}/k_{\text{D}} = 9$) and concluded that the benzylic C–H cleavage is the rate-limiting step (see ESI). This strong KIE is significantly larger than that of the non-metal-based radical reactions and suggests that the C–H abstraction is mediated by the vanadium catalyst instead of a non-metal-based radical.²⁶

Toste recently reported that chiral vanadium complexes can be used for kinetic resolution of secondary alcohols under similar conditions.²⁷ Since $\text{Cp}_2\text{VCl}_2/\text{TBHP}$ is also capable of catalyzing the oxidation of benzylic alcohol, we decided to determine the relative reactivity of $\text{Cp}_2\text{VCl}_2/\text{TBHP}$ toward benzylic C–H versus alcohol oxidation (Scheme 2). Interestingly, oxidation of secondary alcohol **7** gave 26% yield of the benzylic C–H oxidation product **8** and 11% yield of the alcohol oxidation product **9** after 3 days. A shorter reaction time was used to prevent over-oxidation. Likewise, oxidation of primary alcohol **10** gave 34% yield of benzylic C–H oxidation product **11** and 9% yield of alcohol oxidation product **12**. These results suggest that Cp_2VCl_2 catalyzes benzylic C–H oxidation slightly more favorably.

Conclusions

Vanadium complexes have been used extensively for olefin and alcohol oxidation. However, their application in C–H oxidation has not been extensively studied. We demonstrate herein that vanadium complexes can be used to catalyze benzylic C–H oxidation effectively and selectively. Using 1 mol % Cp_2VCl_2 and 5 equiv TBHP, the benzylic $\text{C}(\text{sp}^3)\text{--H}$ groups can be oxidized at 30 °C in good yields without aromatic $\text{C}(\text{sp}^2)\text{--H}$ oxidation. The selectivity of this catalyst system is complementary to that of Mimoun's complex and iron catalysts. The catalyst loading required for this reaction is also significantly lower than most other systems. Under these conditions, alcohols could also be oxidized but at a lower rate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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22. Anhydrous TBHP in *n*-hexane or decane can also be used but the rate of oxidation is lower. Other ineffective oxidants include: O₂, PhIO, PhI(OAc)₂, PhI(TFA)₂, DDQ, NMO, Oxone, TBA-Oxone,

(NH₄)₂S₂O₈, K₂S₂O₈, *m*-CPBA, benzoyl peroxide, NaIO₄ and H₅IO₆. It should be noted that PhIO promoted a slow background benzylic oxidation without any catalyst at room temperature, presumably through a SET pathway similar to the IBX-mediated benzylic oxidation (see Ref. 13b).

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Fig. 1.
Olefin versus C-H oxidation.

Fig. 2.
Proposed mechanism of the Cp₂VCl₂-catalyzed benzylic oxidation.

Scheme 1.
Evidence for the intermediacy of a benzylic alcohol.

Scheme 2.
C–H versus alcohol oxidation.

Table 1Development of the vanadium-catalyzed benzylic oxidation^a

Entry	Catalyst	Oxidant	Time	Yield ^b
1	VO(acac) ₂	5 equiv TBHP(aq)	5 days	82%
2	VOF ₃	5 equiv TBHP(aq)	5 days	79%
3	VOCl ₃	5 equiv TBHP(aq)	5 days	79%
4	VO(O ⁱ Pr) ₃	5 equiv TBHP(aq)	5 days	61%
5	V ₂ O ₅	5 equiv TBHP(aq)	5 days	27%
6	Cp₂VCl₂	5 equiv TBHP(aq)	5 days	87–90%^c
7	Cp ₂ VCl ₂	4 equiv TBHP(aq)	5 days	54%
8	Cp ₂ VCl ₂	3 equiv TBHP(aq)	5 days	25%
9	Cp ₂ VCl ₂	5 equiv TBHP(aq)	3 days	61%
10 ^d	Cp ₂ VCl ₂	5 equiv TBHP(aq)	5 days	84%
11	Cp ₂ VCl ₂	5 equiv H ₂ O ₂ (aq)	5 days	0%
12	Cp ₂ VCl ₂	5 equiv NaClO(aq)	5 days	0%

^a All reactions were conducted with 1 mmol of **1**.^b Determined by GC using dodecane as the external standard with calibration.^c Isolated yields from 4 runs, 86% GC yield.^d With 0.2 mL of CH₃CN.

Table 2

Scope of the Cp_2VCl_2 -catalyzed benzylic oxidation^a

$ \begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{Ar} \quad \text{R} \end{array} \xrightarrow[\text{neat, 30 }^\circ\text{C, 5 days}]{\substack{1 \text{ mol } \% \text{ Cp}_2\text{VCl}_2 \\ 5 \text{ equiv TBHP(aq)}}} \begin{array}{c} \text{O} \\ \parallel \\ \text{Ar} - \text{C} - \text{R} \end{array} $		
Entry	Ar R Yield ^b	Product
1	Ph CH ₃ 90%	
2	4-F-Ph CH ₃ 91%	
3	4-Cl-Ph CH ₃ 86%	
4	4-Me(O)C-Ph CH ₃ 89%	
5	4-NC-Ph CH ₃ 77%	
6	4-MeO-Ph CH ₃ 57%	
7	3-NC-Ph CH ₃ 85%	
8	3-HO ₂ C-Ph CH ₃ 91%	

$ \begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{Ar} \quad \text{R} \end{array} \xrightarrow[\text{neat, } 30^\circ\text{C, 5 days}]{\begin{array}{c} 1 \text{ mol \% Cp}_2\text{VCl}_2 \\ 5 \text{ equiv TBHP(aq)} \end{array}} \begin{array}{c} \text{O} \\ \parallel \\ \text{Ar} - \text{C} - \text{R} \end{array} $			
Entry	Ar	R	Yield ^b
9		3-Br-Ph	CH ₃ 90%
10		3-MeO-Ph	CH ₃ 80%
11		2-Cl-Ph	CH ₃ 52%
12		2-MeO-Ph	CH ₃ 68%
13		4-Et-Ph	CH ₃ 86% ^c
14		4-Ph-Ph	H 54% 60% ^d
15		Ph	<i>n</i> -C ₇ H ₁₅ 57%
16		4-Br-Ph	<i>n</i> -C ₆ H ₁₃ 51%

$ \begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{Ar} \quad \text{R} \end{array} $			$ \xrightarrow[\text{neat, 30 } ^\circ\text{C, 5 days}]{\substack{1 \text{ mol \% Cp}_2\text{VCl}_2 \\ 5 \text{ equiv TBHP(aq)}}} $	$ \begin{array}{c} \text{O} \\ \parallel \\ \text{Ar} \text{---} \text{C} \text{---} \text{R} \end{array} $
Entry	Ar	R	Yield ^b	Product
17	4-MeO-Ph	<i>n</i> -C ₂ H ₅	49%	
18	3-MeO-Ph	<i>n</i> -C ₆ H ₁₃	50%	
19	Ph	CH ₂ C(OH)(CH ₃) ₂	50% ^e	
20	Ph	Ph	95%	

^a All reactions were conducted with 1 mmol of the substrate.

^b Isolated yield.

^c With 2 mol% Cp₂VCl₂ and 10 equiv TBHP.

^d With acetonitrile (0.2 mL).

^e Yield obtained after TBS protection of the alcohol.