# Catalytic hydroxylation of benzene and cyclohexane using in situ generated hydrogen peroxide: new mechanistic insights and comparison with hydrogen peroxide added directly

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## Abstract

Hydrogen peroxide is considered an ideal "green" oxidant due to its high oxidizing ability and lack of toxic by-products. Herein, we report on an oxidation procedure that couples metallic palladium-catalyzed in situ hydrogen peroxide generation from dihydrogen and dioxygen with a second vanadium or iron catalyst that utilizes the hydrogen peroxide for the hydroxylation of benzene and cyclohexane. Studies indicate that the slow step in the overall reaction is the formation of usable hydrogen peroxide, and the mechanism of hydroxylation by the second catalyst is not affected by the presence of metallic palladium. The reported procedure, which resembles monoxygenases, allows the direct use of dioxygen in catalytic oxidations. Comparisons between the in situ method of hydrogen peroxide generation and hydrogen peroxide added via syringe pump show that the in situ method is more selective. Additionally, new insight into the mechanism of vanadium-catalyzed benzene hydroxylation is reported. Mechanistic investigations include the observation of a high NIH shift, the use of a radical cation rearrangement probe, and the first use of $H_2{}^{18}O$ enrichment studies. Based on these, an electron transfer mechanism resulting in a radical cation intermediate is proposed.
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## 1. Introduction

Dioxygen is the ideal oxidant from both environmental, as well as economical, standpoints. However, dioxygen rarely participates in selective, catalytic, oxidation of organic substrates. A second, albeit more expensive, green oxidant is hydrogen peroxide—a strong oxidizing agent which shows good selectivity for many oxidations, and produces water as the only by-product [1]. Despite its potential value as an oxidant, hydrogen peroxide has some serious drawbacks [2]. It is inherently corrosive and, especially in high concentrations, is prone to catalytic decomposition. Using dilute aqueous solutions can minimize these problems; however, the excess water often produces a biphasic mixture with the organic substrate and the oxidant residing in different phases.

The palladium-catalyzed formation of hydrogen peroxide from dihydrogen/dioxygen and carbon monoxide/dioxygen/water mixtures has been previously reported (with peroxide concentrations determined using colorimetric titrations) [3–6]. Furthermore, we [7,8] and others [9–12] have previously utilized the in situ generation of hydrogen peroxide to

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carry out palladium-catalyzed oxidations. Others have also shown that hydrogen peroxide generated using palladium can be used with another heterogeneous catalyst including copper [12–15], titanium [16], and vanadium [17] to carry out organic oxidations. None of these systems involved a homogeneous oxidation catalyst and were not compared to the corresponding system where hydrogen peroxide is added directly. We are prompted to publish our work by a recent report on the oxidation of benzene with supported platinum, hydrogen, and oxygen in the presence of homogeneous catalysts [18]. There are, however, no mechanistic details in this paper.

Herein, we report on an oxidation procedure that couples palladium-catalyzed in situ hydrogen peroxide generation from dihydrogen and dioxygen with a second homogeneous catalyst that utilizes the hydrogen peroxide for the hydroxylation of organic substrates. This procedure, which resembles monoxygenases, allows the direct use of dioxygen in catalytic oxidations that normally use hydrogen peroxide. In principle, the hydrogen peroxide is formed slowly, allowing its efficient use in substrate oxidation and avoiding overoxidation. The amount of water in the reaction mixture is minimized since it arises solely from the reaction. The above procedure is also compared to the same reaction where hydrogen peroxide is added slowly via a syringe pump.

In an effort to show that the palladium merely acts as a hydrogen peroxide generator and does not participate in the substrate oxidation, we have investigated mechanistic aspects of the oxidations with an emphasis on vanadium-catalyzed benzene oxidation. The data obtained indicates that this is indeed the case. Further mechanistic investigations including the use a radical cation rearrangement probe and the first use of $H_2^{18}O$ enrichment studies have led us to propose an electron transfer mechanism resulting in a radical cation intermediate.

## 2. Results

We have employed supported metallic palladium as the catalyst for in situ hydrogen peroxide generation from dihydrogen and dioxygen. Our results for the oxidation of benzene are summarized in Table 1. In every case, the molar ratio of dihydrogen to dioxygen was 1. An excess of dinitrogen was added to keep the gas mixture below flammability limits. Table 1, entry 1 shows that very little oxidation occurs in the absence of the second, hydroxylating catalyst. Control experiments show that V(acac)$_3$ (acac = acetylacetonate) will catalyze the hydroxylation of benzene by hydrogen peroxide, even in the absence of metallic palladium, dihydrogen and dioxygen. Furthermore, no oxidation occurs when the vanadium hydroxylation catalyst is used without some source of hydrogen peroxide (Table 1, entry 4) or when vanadium catalyst is exposed to hydrogen and oxygen in the absence of palladium. Thus, metallic palladium is active in the formation of hydrogen peroxide, which in turn gen-

Table 1
Yields for several vanadium and iron catalysts for benzene oxidation[a]

| Entry | Hydroxylation catalyst | Turnovers (h)[b] | Phenol (mmol) | Benzoquinone (mmol) |
|---|---|---|---|---|
| 1 | None | – | 0.003(6) | – |
| 2 | V(acac)$_3$ | 70 | 0.45(4) | – |
| 3 | V(O)(acac)$_2$ | 68 | 0.44(2) | – |
| 4 | V(O)(acac)$_2$[c] | 0 | 0.00 | – |
| 5 | VO(O$_2$)(2-picolinate)(H$_2$O)$_2$ | 55 | 0.4(1) | – |
| 6 | tris(Dibezoylmethanato)Fe(III) | 41 | 0.26(5) | 0.05(1) |
| 8 | Fe(II) acetate | 28 | 0.18(4) | 0.03(1) |
| 9 | Fe(II)Cl$_2$·4H$_2$O | 39 | 0.27(8) | 0.05(1) |

[a] Reactions were performed using the catalyst noted (3.2 μmol), 5% Pd on Al$_2$O$_3$ (20.0 mg), benzene (2 ml), and glacial acetic acid (2.5 ml). The reactions were performed in glass liners in 300 ml stainless steel autoclaves with H$_2$ (100 psi; 82 mmol), N$_2$ (1000 psi), and O$_2$ (100 psi; 82 mmol) at 65 °C for 2 h. Values listed are the average of at least two runs.

[b] mmol phenol/mmol catalyst (V or Fe)·h.

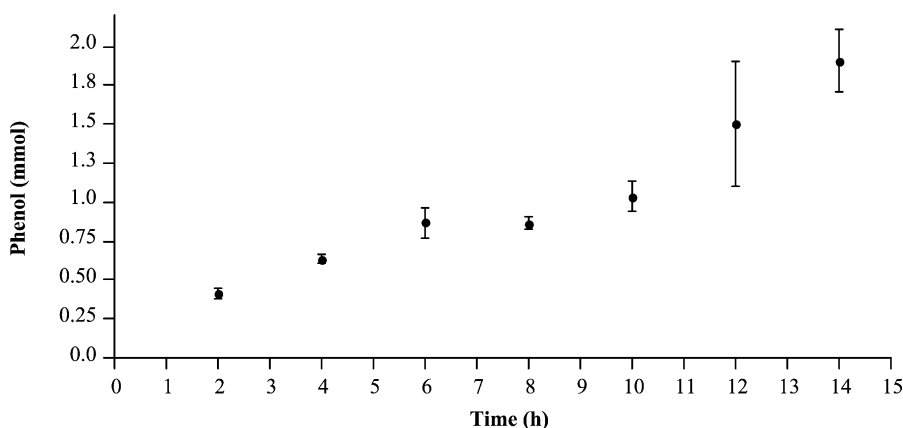[c] 0.16 mmol catalyst with no palladium, dihydrogen, or dioxygen present.

Fig. 1. The amount of phenol produced vs. reaction time. Benzene (2 ml) was allowed to react with V(acac)$_3$ (3.2 µmol), 5% Pd on Al$_2$O$_3$ (20.0 mg) in glacial acetic acid (2.5 ml). Reactions were run in glass liners in 300 ml stainless steel autoclaves under an atmosphere consisting of H$_2$ (100 psi; 82 mmol), N$_2$ (1000 psi), and O$_2$ (100 psi; 82 mmol) for the indicated amount of time. Reactions were repeated at least twice and the data here is an average.

erates an active catalytic species from the vanadium complex. It is apparent from the similar reactivity observed for entries 2 and 3, Table 1, that the same active species is generated from the two starting vanadium complexes. That the actual oxidant is not the oxo group in V(O)(acac)$_2$ is shown by control experiments where an excess of this compound failed to oxidize benzene in the absence of dihydrogen and dioxygen though it has proved effective in oxidation of other substrates [19].

The results of running the experiment shown in entry 2, Table 1, for an extended period of time are shown in Fig. 1. The linear increase in the concentration of phenol with time suggests that the catalytic system is relatively long lived under these conditions.

Finally, as shown in Table 1, several iron species are also effective catalysts for the oxidation of benzene with in situ generated hydrogen peroxide. However, both the activities and selectivities are lower than that for the corresponding vanadium complexes.

Benzene was reacted in lower concentrations to better determine the selectivity and conversion using in situ generated hydrogen peroxide (Table 2), as well as with hydrogen peroxide added directly by syringe pump under analogous conditions (Table 3). When hydrogen peroxide is made in situ the selectivity

Table 2

Conversion and selectivity to phenol using lower initial benzene concentration in situ hydrogen peroxide generation[a]

| Entry | Hydroxylation catalyst | Benzene (mmol) | Phenol (mmol) | Benzoquinone (mmol) | Conversion to phenol (%) | Selectivity to phenol (%)[b] |
|---|---|---|---|---|---|---|
| 1 | V(acac)$_3$ | 1.4 | 0.20(1) | tr. | 14 | >99 |
| 2[c] | V(acac)$_3$ | 1.4 | 0.15(2) | tr. | 10 | >99 |
| 3 | V(acac)$_3$ | 0.52 | 0.13(1) | tr. | 26 | >99 |
| 4[d] | V(acac)$_3$ | 0.52 | 0.10(1) | 0.0021(6) | 21 | 99 |
| 5 | tris(Dibezoylmethanato)Fe(III) | 1.4 | 0.059(9) | 0.0017(2) | 4.2 | 97 |

[a] Reactions were run using the amount of benzene indicated with V(acac)$_3$ or tris(dibenzoylmethanato)Fe(III) (3.2 µmol) and 5% Pd/Al$_2$O$_3$ (20.0 mg) in acetic acid (4.4 ml) under an atmosphere of H$_2$ (100 psi; 82 mmol), N$_2$ (1000 psi), and O$_2$ (100 psi; 82 mmol) in a 300 ml autoclave for 2 h at 65 °C. Reactions were repeated at least two times and the data listed is an average.

[b] Selectivity calculated as mmol phenol/(mmol phenol + mmol benzoquinone).

[c] Using 2.4 ml of acetic acid.

[d] Four hours reaction time.

Table 3
Oxidation of benzene using hydrogen peroxide added via a syringe pump[a]

| Entry | Hydroxylation catalyst | Benzene (mmol) | Phenol (mmol) | Benzoquinone (mmol) | Conversion to phenol (%) | Selectivity (%)[b] | $H_2O_2$ efficiency (%) |
|---|---|---|---|---|---|---|---|
| 1 | V(acac)$_3$ | 22 | 0.60(3) | 0.19(1) | 2.7 | 76 | 20 |
| 2 | V(acac)$_3$ | 5.9 | 0.22(6) | 0.041(2) | 3.7 | 84 | 6.2 |
| 3[c] | V(acac)$_3$ | 5.9 | 0.0050 | 0.0063 | 0.08 | 7.3 | 0.36 |
| 4 | V(acac)$_3$ | 0.52 | 0.047(3) | 0.012(2) | 9.0 | 80 | 1.4 |
| 5 | tris(Dibezoylmethanato)Fe(III) | 5.9 | 0.0097 | tr. | 0.16 | 69 | 0.37 |
| 6 | tris(Dibezoylmethanato)Fe(III) | 0.52 | 0.0017 | 0.001 | 0.33 | 64 | 0.075 |

[a] Reactions were run using 3.2 μmol of the catalyst indicated, benzene (amount indicated), and acetic acid (to make total volume 4.5 ml) for 2 h at 65 °C. During this time 0.28 ml, 4.9 mmol of 50% $H_2O_2$ (diluted to 0.68 ml total with acetic acid) was added dropwise via a syringe pump. Reactions were repeated and values listed are the averages except entries 3, 5, and 6.
[b] Selectivity calculated as mmol phenol/(mmol phenol + mmol benzoquinone).
[c] 2.6 mmol CBrCl$_3$ used as a potential radical trap.

for phenol versus benzoquinone is remarkably good even at relatively high conversion (26%). Reducing the amount of solvent (entry 2) or increasing reaction time (entry 4) did not improve yields further. Instead, there is some loss in selectivity. Use of an iron catalyst (entry 5) results in both lower selectivity and conversion.

The selectivity for phenol over benzoquinone in these vanadium-catalyzed reactions, compared to those where hydrogen peroxide was added via syringe pump (see below), warrants further comment. Even at long reaction times, benzoquinone was not observed when benzene was present in excess (Table 1) and was minimal under conditions of high conversion (Table 2). Additionally, the amount of carbon dioxide generated in the reaction was below measurable limits. Carbon dioxide remained below measurable limits even when reactions were run for 4 h with less starting benzene (0.52 mmol).

Table 3 shows the results when hydrogen peroxide is added directly to the reaction via a syringe pump over 2 h. In these reactions one can see that the selectivity for phenol versus benzoquinone is markedly lower for both the vanadium and iron catalysts. This is even true with roughly five times the amount of benzene present! Also, in these reactions the conversion is lower compared to the in situ reactions. It should be pointed out that less oxidant was used here than what is typically generated during the reactions shown in Tables 1 and 2 (see Fig. 2) due to the problem of immiscibility from the extra water added. The oxidant efficiency was found to increase significantly with increasing amount of substrate employed, suggesting
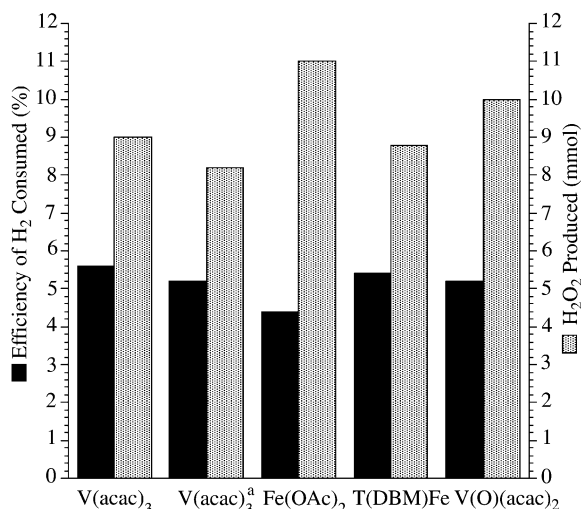


Fig. 2. Percentage of dihydrogen consumed which is used in the oxidation of benzene to products (phenol and benzoquinone) using vanadium and iron catalysts. Efficiency is calculated from the total water produced in the reaction vs. the amount of products made. It is assumed that for every mole of hydrogen peroxide formed, 1 mol of water is generated either through hydrogen peroxide decomposition or through substrate oxidation. Reactions were run using 3.2 μmol of the catalyst indicated, 5% Pd on Al$_2$O$_3$ (20.0 mg), benzene (2 ml), and acetic acid (2.5 ml), exposed to H$_2$ (100 psi), N$_2$ (1000 psi), and O$_2$ (100 psi) for 2 h at 65 °C in glass liners in a 300 ml autoclave. Each data point is the average of four reactions. Abbreviations: OAc, acetate; T(DBM), tris(dibenzoylmethanato). The letter (a) indicates that the reactions were performed using 10.0 mg of 5% Pd on Al$_2$O$_3$.

that hydrogen peroxide decomposition occurs in parallel with substrate oxidation.

One interesting observation that came out of the comparison is the significantly higher selectivity for phenol using in situ generated hydrogen peroxide when compared to hydrogen peroxide added directly by syringe pump. Of course, it is not possible to employ exactly analogous conditions for the two sets of experiments since the rate of in situ generation of hydrogen peroxide is not known; however, the hydrogen peroxide was added dropwise over the course of the experiment. It should be pointed out that the selectivities shown in Tables 2 and 3 are phenol over benzoquinone (the only other product observed in significant amounts). Attempts to quantify reaction selectivity for phenol based on benzene consumption proved difficult due to the volatility of the reaction mixture, particularly when dealing with reactions under pressure. Nevertheless, approximate conversion numbers were obtained for one example each of in situ and the syringe pump reactions. These reactions employed 0.50 mmol of benzene and corresponded in conditions to entry 3, Table 2 and entry 4, Table 3. For the in situ reaction a value of 49 (8)% was obtained, and for the syringe pump reaction a value of 31 (4)% was found. Although these values are markedly lower than those obtained when comparing only to benzoquinone, the in situ method still remains significantly more selective. We were unable to identify the unknown products; however, biphenyls, $\alpha,\omega$-diacids, and carbon dioxide were not observed as reaction products.

In another attempt to address the selectivity of the reactions, direct competition reactions were attempted between benzene and phenol in various ratios. These reactions also proved problematic due to the hydrogenation of phenol to cyclohexanone under these conditions (in order to avoid flammable gas mixtures, dihydrogen has to be added to the reaction mixture prior to the addition of dioxygen). The hydrogenation occurs only when hydrogen is present in the absence of oxygen—an observation confirmed using a control where a combination of benzene and phenol was exposed to only hydrogen and produced cyclohexanone from phenol. Interestingly, this product was only observed in trace quantities under any other reaction condition attempted. Thus, under the actual reaction conditions, a competition must exist for the formation

of hydrogen peroxide versus hydrogenation of phenol by palladium metal.

The effect of bromotrichloromethane, a radical trap, on benzene oxidation was probed. A comparison of entries 2 and 3 shows that bromotrichloromethane significantly reduces the amount of oxidation. Several unknown products in trace quantities were observed. However, there was no detectable amount of the expected radical trap products, halobenzenes. One explanation for this result is that though phenyl radical is absent in the reaction, other radical reactions such as those centered on the vanadium may be operating. Note that palladium was excluded from these reactions.

Returning to reactions involving in situ hydrogen peroxide generation, the reaction efficiency remains relatively constant regardless of the second oxidation catalyst employed (Fig. 2). Starting with 82 mmol each of dihydrogen and dioxygen, ca. 9–10 mmol of hydrogen peroxide is formed in 2 h under the reaction conditions. However, only ca. 5–6% of the hydrogen peroxide generated is actually used for phenol and benzoquinone formation. This suggests that palladium is primarily responsible for the decomposition of hydrogen peroxide since one would expect more variations if the second catalysts played a significant part in the decomposition. A comparison with the literature shows that in general hydrogen peroxide oxidation of benzene is more efficient, depending critically on catalyst and reaction conditions [17,20,21]. The gas-phase oxidation of benzene using in situ generated hydrogen peroxide, however, is around 6% efficient [22].

An interesting observation was made when the effect of vanadium loading was investigated. As Fig. 3 shows, the amount of phenol generated increases rapidly with increasing vanadium loading until a plateau is reached. A large increase in vanadium concentration beyond this point, results in decreased phenol production. On the basis of previous reports [19,23], it appears that the drop-off in activity may be due to an equilibrium between the catalytically active monomeric vanadium species and an inactive $\mu$-oxo dimer; the latter being favored at higher vanadium concentrations.

Finally, the amount of the solvent, acetic acid, was varied in benzene oxidation. It was found that even with smaller amounts of acetic acid, the reaction involving V(acac)$_3$ gives similar results. Thus, acetic
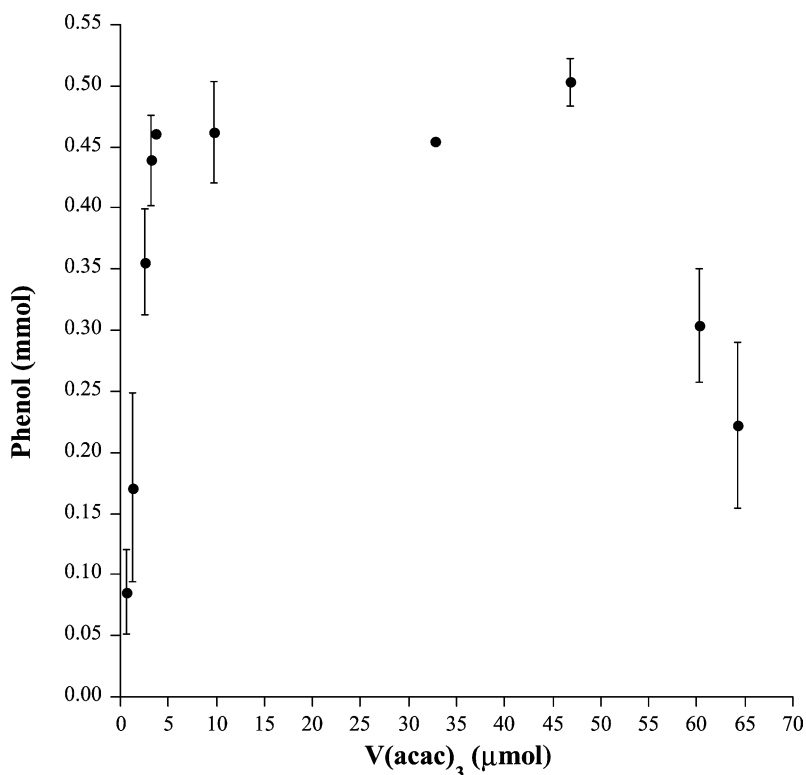
Fig. 3. Amount of phenol generated vs. vanadium loading. Reactions were performed using benzene (2 ml), glacial acetic acid (2.5 ml), and 5% Pd on $Al_2O_3$ (20.0 mg) exposed to $H_2$ (100 psi), $N_2$ (1000 psi), and $O_2$ (100 psi) for 2 h at 65 °C in glass liners in a 300 ml autoclave. Each data point is the average of two reactions unless indicated.

acid serves merely to make the water formed in the course of the reaction miscible with benzene. Indeed, with *no* acetic acid present, the reaction proceeds with only a slight decrease in activity attributable to the resultant biphasic nature of the reaction media. The fact that the reaction proceeds in the absence of acetic acid

eliminates the possible intermediacy of peracid radical species [24].

Table 4 shows some representative examples of cyclohexane oxidation. Because of GC peak overlap, propionic acid was chosen as the solvent for this substrate; however, control experiments indicate that,

Table 4
Yields for selected cyclohexane oxidation catalysts using in situ hydrogen peroxide[a]

| Entry | Hydroxylation catalyst | Turnovers (h)[b] | Cyclohexanol (mmol) | Cyclohexanone (mmol) |
|---|---|---|---|---|
| 1 | tris(Dibenzoylmethanato)Fe(III) | 17 | 0.07(2) | 0.021(3) |
| 2 | Fe(II) acetate | 32 | 0.13(2) | 0.040(7) |
| 3 | V(O)(acac)$_2$ | 25 | 0.08(1) | 0.040(5) |
| 4 | V(acac)$_3$ | 38 | 0.14(5) | 0.05(2) |

[a] Reactions were performed using the catalyst noted (3.2 μmol), 5% Pd on $Al_2O_3$ (20.0 mg), cyclohexane (1.5 ml), and propionic acid (3 ml). The reactions were performed in glass liners in 300 ml stainless steel autoclaves with $H_2$ (100 psi; 82 mmol), $N_2$ (1000 psi), and $O_2$ (100 psi; 82 mmol) at 36 °C for 2 h. Values listed are the average of at least four runs.
[b] [mmol cyclohexanol + 2 × (mmol cyclohexanone)]/mmol catalyst (Fe or V)·h.

unlike acetic acid, there is some oxidation of the solvent. The vanadium and iron compounds tested show similar rates for cyclohexane oxidation. An interesting observation is that both systems exhibit a significantly higher selectivity towards the alcohol over the ketone. The preponderance of cyclohexanol is noteworthy and suggests that cyclohexyl radicals are not involved in the oxidation. Alkyl radicals react with dioxygen at diffusion-controlled rates forming peroxy radicals which then undergo Russell radical termination to form a 1:1 mixture of alcohol and ketone [25,26]. Since the alcohol can be further oxidized to the ketone, radical-mediated alkane oxidations in the presence of dioxygen invariably result in product mixtures with alcohol to ketone ratio of 1. It should be pointed out that the presence of a metal in solution can alter this ratio via the metal-catalyzed decompositions shown in Eqs. (1) and (2) [27]:

$$ROOH + M^{n+} \rightarrow RO^{\bullet} + HO^{-} + M^{(n+1)+} \qquad (1)$$

$$ROOH + M^{(n+1)+} \rightarrow ROO^{\bullet} + H^{+} + M^{n+} \qquad (2)$$

As a further probe for radicals, product mixtures from cyclohexane oxidation were analyzed both before and after the addition of triphenylphosphine. This species quantitatively converts cyclohexyl hydroper-

oxide to cyclohexanol [28,29]. For all the catalysts employed, there was no difference in the composition of the product mixture before and after the addition of triphenylphosphine. Thus, free cyclohexyl hydroperoxide, derived from the reaction of cyclohexyl radical with dioxygen, does not appear to be present.

As the amount of cyclohexane is lowered, the ratio of cyclohexanol to cyclohexanone becomes equal to and then eventually favors the formation of the ketone over the alcohol. This result is not surprising since palladium is a known catalyst for the aerobic oxidation of alcohols and ketones [30–33]. Metallic palladium clusters have been known to perform similar oxidations in the presence of an oxidant [34].

One key issue in bimetallic hydrocarbon oxidations is the identity of the rate determining step. As shown in Fig. 4, for a given vanadium concentration, the yield of phenol increases linearly with increasing amount of metallic palladium. This suggests that the slow step is the in situ generation of hydrogen peroxide under these conditions. Other lines of evidence suggest that this is indeed true for all the oxidations described here. As Fig. 5 shows, the energy of activation is similar regardless of the hydroxylation catalyst or the substrate. Thus, the values obtained are 5(1), 6(1), and 5(1) kcal/mol for the hydroxylation of
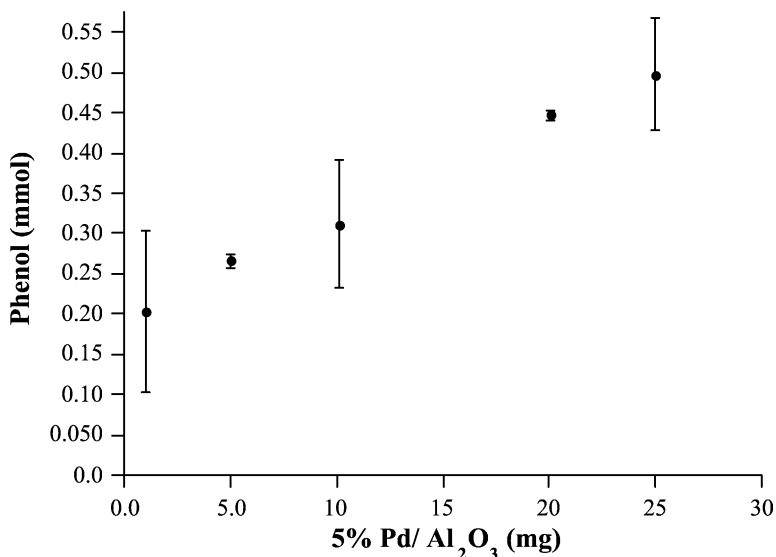


Fig. 4. Amount of phenol generated vs. palladium loading. Reactions were run using benzene (2 ml), glacial acetic acid (2.5 ml), V(acac)$_3$ (3.2 µmol), and 5% Pd on Al$_2$O$_3$ exposed to H$_2$ (100 psi; 82 mmol), N$_2$ (1000 psi), and O$_2$ (100 psi; 82 mmol) for 2 h at 65 °C in glass liners in a 300 ml autoclave. Each data point is the average of two reactions.
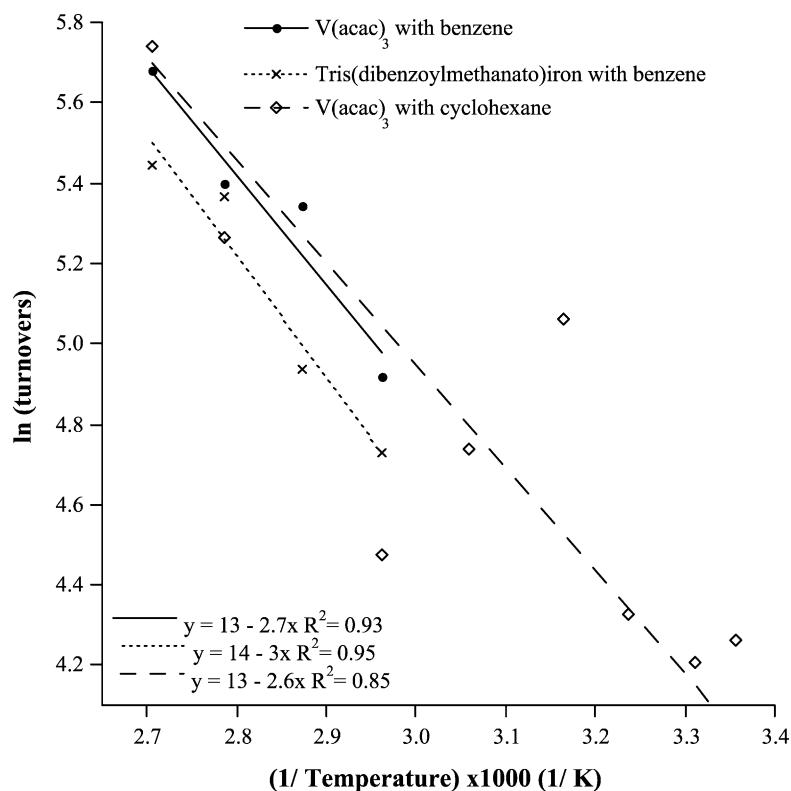
Fig. 5. Arrhenius plots for two catalysts and two substrates. For reactions with benzene, benzene (2 ml) was allowed to react with $V(acac)_3$ (3.2 μmol) or tris(dibenzoylmethanato) iron (3.2 μmol), 5% Pd on $Al_2O_3$ (20.0 mg) in glacial acetic acid (2.5 ml). For reactions with cyclohexane, cyclohexane (1.5 ml) was allowed to react with $V(acac)_3$ (3.2 μmol), and 5% Pd on $Al_2O_3$ (20.0 mg) in propionic acid (3 ml). Reactions were run in glass liners in 300 ml stainless steel autoclaves under an atmosphere consisting of $H_2$ (100 psi; 82 mmol), $N_2$ (1000 psi), and $O_2$ (100 psi; 82 mmol) for 2 h. Reactions were repeated at least three times and the data here is an average.

benzene with $V(acac)_3$, the hydroxylation of benzene with tris(dibenzoylmethanato)Fe(III), and the hydroxylation of cyclohexane with $V(acac)_3$, respectively. The linear fit observed for cyclohexane oxidation is poorer at higher temperatures; at lower temperatures (data not shown) the fit is comparable to the other two reactions. The activation energy values do not change significantly when the stirring rate is changed, indicating that gas diffusion is not the rate-limiting step [35]. Furthermore, the values are close to that calculated from a report of gas-phase benzene to phenol oxidation by a Pd-Cu composite catalyst, carried out around 200 °C, in the presence of dihydrogen and dioxygen: 6 kcal/mol [22].

Using a 1:1 ratio of $C_6D_6$ and $C_6H_6$, no significant isotope effect ($k_H/k_D$) was observed indicating that C–H bond-breaking is not the rate determining step in the reaction. While this may suggest that the slow step is the in situ generation of hydrogen peroxide, the absence of an isotope effect has also been reported previously for benzene hydroxylation using vanadium complexes [36], $O(^3P)$ atoms [37], and trifluoroperacetic acid [38].

In the corresponding oxidation of toluene, the ratio of products derived from benzylic versus nuclear attack was 1:2.6. Given the lower homolytic bond dissociation energy of benzylic C–H bonds compared to aromatic C–H bonds (88 kcal/mol versus 111 kcal/mol), this suggests that the C–H activation step does not involve hydrogen atom abstraction and indicates the presence of a strongly electrophilic oxidant [23]. This is similar in magnitude to that observed in the stoichiometric $V(O)(O_2)(2\text{-picolinate})(H_2O)_2$ reaction [36]. The product distribution for the cresols

derived from toluene was 38:22:40 for the *o*-, *m*-, and *p*-isomers, respectively. This ratio is again similar to that reported for stoichiometric vanadium picolanato system (48:20:32) [36] and for the catalytic hydrogen peroxide oxidation using the same catalyst (58:19:23) [20]. Shul'pin et al. [39] have also seen similar results (54:12:34) with another vanadium/hydrogen peroxide system.

Finally, by using $p$-CH$_3$-C$_6$H$_4$-D as the substrate, an NIH shift value of 90% deuterium retention in the *p*-cresol product was observed. High values have been observed for arene oxidations by the V(O)(O$_2$)(2-picolinate)(H$_2$O)$_2$ complex [36] and by the monooxygenase, cytochrome P$_{450}$ [40].

Use of excess ^{18}O-enriched water yielded significant [18]O incorporation into phenol during benzene oxidation with anhydrous hydrogen peroxide (added as urea complex) and V(acac)$_3$. A value of 39 (2)% was obtained over two runs. This value corresponds to approximately 43% of the maximum possible [18]O incorporation into the phenol product.[1]

Reasoning that the incorporation of water might be from a nucleophilic attack, excess tetramethylammonium chloride was added to the reaction mixture. No chlorobenzene was detected with aqueous hydrogen peroxide as an oxidant. However, a decrease in activity and much poorer selectivity for phenol (37%) were observed. Separate experiments showed that the presence of halides in the reaction mixture decreases reactivity in the order Cl$^-$ < Br$^-$ < I$^-$. When an anhydrous solution of hydrogen peroxide was added via the urea complex dissolved in acetic acid (only water present being that in the solvent and what is formed be peroxide decomposition), no reaction was observed. These observations show that although water is incorporated into the product, it is not acting as a nucleophile.

Cyclopropylbenzene has been reported as a good probe for the intermediacy of radical cations [41]. The cyclopropyl group forms ring-opened products in a radical cation mechanism but remains closed in purely radical or direct hydroxylation pathways. In the vanadium-catalyzed oxidation of cyclopropylbenzene with syringe-pumped hydrogen peroxide, the three main products were ring-opened while a fourth appears to be a hydroxyphenylcyclopropane. Of the three main products, the one present in the greatest quantities is 3-hydroxy-1-phenyl-propanan-1-one, based on GC retention time and fragmentation pattern. Another product was positively identified as benzaldehyde. We were unable to identify the third product, but based on its fragmentation pattern, it appears that it is a ring-opened product.

The product analysis in reactions where hydrogen peroxide is generated in situ proved more difficult due to substantial palladium-catalyzed cyclopropyl ring hydrogenation [42]. When cyclopropylbenzene was reacted with vanadium catalyst in the presence of in situ generated hydrogen peroxide, excluding propylbenzene and propylbenzene derived products, two of the main products appear to be hydroxyphenylcyclopropane isomers while a third product is the ring-opened product, 3-hydroxy-1-phenyl-1-propan-1-one. Again, benzaldehyde is identified here; in this case it is also a potential product of propylbenzene oxidation.

## 3. Discussion

Several key issues need to be addressed in the bimetallic hydrocarbon oxidation system that involves the in situ generation of hydrogen peroxide. These are (a) the identity of the rate-limiting step and (b) the mechanism of the hydroxylation reaction and whether it differs from that observed for similar oxidations where the hydrogen peroxide is added directly. These are discussed below.

The first issue involves the identity of the rate-limiting step. As shown in Fig. 4, for a given vanadium concentration, the yield of phenol increases linearly with increasing amount of metallic palladium. This suggests that the slow step is the in situ generation of hydrogen peroxide under these conditions. Fig. 5, which encompasses two different hydroxylating catalysts and substrates, also supports this claim. Thus, since all the reactions possess nearly identical activation energies regardless of catalyst or substrate (the C–H bond dissociation energies are quite different), and a mass transfer effect seems unlikely

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[1] The corrected value was obtained by accounting for the amount of H$_2$[16]O present in the reaction mixture. The sources included the amount of H$_2$[16]O from hydrogen peroxide (produced either from decomposition or substrate oxidation), the H$_2$[16]O present in 95% H$_2$[18]O used, and the residual H$_2$[16]O in the benzene/acetic acid mixture.

(similar values were obtained at different stirring rates), the most logical explanation is that the rate-limiting step is the formation of hydrogen peroxide. It follows that the actual energy of activation for both benzene and cyclohexane oxidation is lower than the values obtained (5–6 kcal/mol).

Fig. 2 indicates that the amount of hydrogen peroxide formed and the efficiency with which it is utilized do not depend significantly on the nature of the second, hydroxylating, catalyst. This suggests that palladium is primarily responsible for the decomposition of hydrogen peroxide and that the rate of hydrogen peroxide formation minus its rate of decomposition limits the overall reaction rate. The higher hydrogen peroxide utilization efficiency in the absence of palladium (see entry 1, Table 3) is also consistent with this hypothesis.

A second issue is whether the hydroxylation mechanism in the presence of in situ generated hydrogen peroxide is different from that observed for similar oxidations with directly added hydrogen peroxide. This is important because one of the goals was to show that hydrogen peroxide generated in situ can be utilized for a variety of known organic oxidations where hydrogen peroxide is the oxidant. Therefore, in order to show that the palladium did not participate in the actual substrate oxidation, the mechanism of vanadium-catalyzed benzene hydroxylation was investigated in some detail and compared with more traditional oxidations that involve directly added hydrogen peroxide. Indeed, the two kinds of systems appear to exhibit similar reaction characteristics. These include the ratio of nuclear to benzylic oxidation, the ratio of isomeric cresols formed, the high NIH shift value, and the absence of a deuterium isotope effect. Based on these similarities, along with the observation that metallic palladium is inactive

the typically observed pathway for benzene hydroxylation by vanadium catalysts.

Having established that the role of palladium is confined to the in situ generation (and decomposition) of hydrogen peroxide, we next turned to the mechanism by which the hydroxylation of the substrate occurs. That hydrogen peroxide alone is not responsible for substrate oxidation was confirmed by control experiments. These results also remove the possibility that radicals formed from acetic acid are responsible for oxidation; a pathway that has been observed previously [24]. This path is further excluded by the fact that benzene oxidation is observed by the palladium/vanadium combination even in neat benzene.

Consequently, the vanadium must play a critical role in the hydroxylations. Several actual oxidants have been proposed. Based on literature precedent, the involvement of a vanadium peroxo species seems likely in these reactions, though it may not be the active oxidant. Similarly, the formation of a vanadium $\mu$-oxo dimer (or similarly bridged oligomers) most likely represents the inactive catalyst form. Such species have been previously surmised [19] and are presumably responsible for the decrease in activity under high catalyst loading (see Fig. 3).

The incorporation of oxygen from $^{18}O$-enriched water into the substrate sheds further light on the nature of the active oxidant. One plausible route to $^{18}O$ incorporation involves an equilibrium with the vanadium peroxo species, as shown in Eq. (3). This would then go on to form the active vanadium(V) oxidant as shown. A similar mechanism involving iron-catalyzed oxidations with hydrogen peroxide has recently been reported [43]. This explanation is also consistent with the observed ~43% $^{18}O$ enrichment in the phenol product since the proposed pathway limits incorporation to ≤50% of the theoretical maximum:
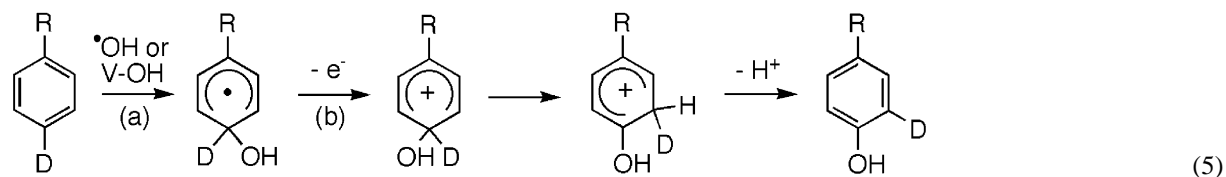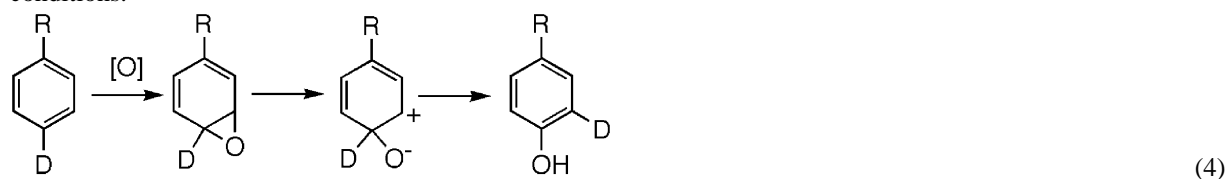


(3)
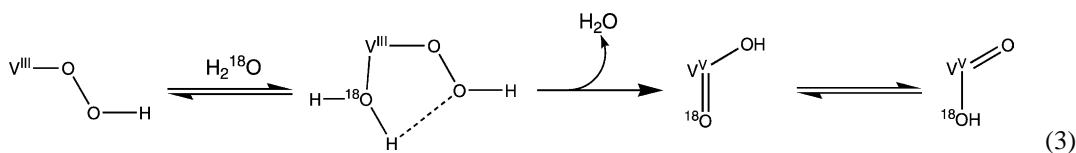
without the simultaneous presence of a second hydroxylation catalyst, a strong case can be made that the presence of metallic palladium or the in situ generation of hydrogen peroxide does not significantly effect

The use of cyclopropylbenzene as a mechanistic probe has been reported previously [44,45]. The cyclopropyl group forms ring-opened products in a radical cation mechanism but remains closed in

purely radical or direct hydroxylation pathways [41]. The observation of ring-opened products when cyclopropylbenzene was oxidized using vanadium catalysts under both in situ hydrogen peroxide generation and direct addition of hydrogen peroxide suggests a radical cation mechanism. It should be noted that a substrate's oxidation potential can influence the mechanism observed in these types of reactions [46,47]. Cyclopropylbenzene is harder to oxidize relative to benzene [47] and, indeed, cyclopropylbenzene was fairly unreactive compared to benzene under our reaction conditions. Thus, the mechanism leading to ring-opened products with cyclopropylbenzene is also likely to operate for benzene itself.

The NIH shift has traditionally been associated with arene oxide intermediates formed from an electrophilic metal oxo complex (Eq. (4)) [48,49]. However, more recent work has shown that this may not always be the case, and that an alternative mechanism which proceeds through a radical cation intermediate is also possible (Eq. (5)) [50–52]. Based on our results with cyclopropylbenzene, we favor the radical cation mechanism for benzene oxidation under our conditions.

The failure to observe halogenated products when bromotrichloromethane was added to the benzene oxidation reaction is consistent with a mechanism that does not involve hydrocarbyl radicals. Such products have been observed in a vanadium/hydrogen peroxide system with cyclohexane as substrate [27]. Our results suggest a direct transfer of a hydroxyl group from the metal to benzene.

It is unclear why bromotrichloromethane causes a sharp decrease in reaction rate (see Table 3). One possible explanation is catalyst deactivation by interaction of a bromide ion or bromine radical with the vanadium center. We have observed that the addition of soluble halide salts resulted in a decrease in catalyst activity in the order $Cl^- < Br^- < I^-$.

Based on the information obtained thus far we propose the mechanism shown in Scheme 1. Several aspects of the mechanism deserve further comment. First, it is not known how the active vanadium species is formed. As shown in Table 1, no difference in activity or selectivity is observed starting with either $V(acac)_3$ or $V(O)(acac)_2$ suggesting that both



$$(4)$$



$$(5)$$

A final mechanistic issue is whether the steps a and b in Eq. (5) may be reversed, i.e. an electron is initially abstracted from benzene to form a discreet radical cation which is followed by hydroxyl addition. Although we do not have any direct evidence for one over the other, it appears that an initial electron transfer is most consistent with the ring-opened products obtained with cyclopropylbenzene. As discussed above, it is also consistent with decreased reactivity observed for cyclopropylbenzene compared to benzene. Furthermore, peroxovanadium complexes have been noted as particularly good one-electron acceptors [53].

compounds go on to form the active species. The oxovanadium(III) species depicted in Scheme 1 is the most logical and plausible starting point based on the experimental evidence collected. The reversible reaction of water with the vanadium(III) peroxo intermediate must be fast in order to account for the ~50% $^{18}O$ enrichment observed in the product phenol. Any exchange of oxygens between the oxo and hydroxo groups in the vanadium(V) species is irrelevant as the $^{18}O$ label has been sufficiently scrambled before that point. The steps following electron transfer to benzene
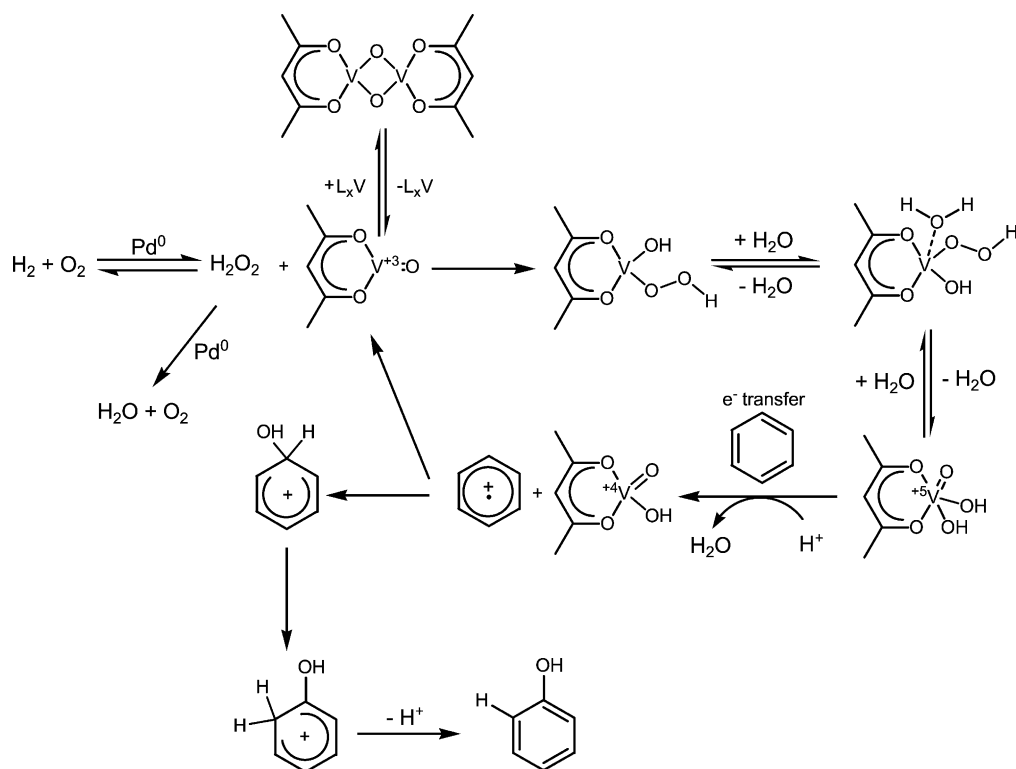
Scheme 1. Possible mechanism for benzene oxidation.

must be fast in order to account for the inherent reaction selectivity. Finally, a significant isotope effect ($k_H/k_D \sim 11$) must exist in the loss of the proton from the final cation to account for the large NIH shift value observed.

## 4. Conclusion

The procedure described above supports the versatility of supported palladium as an in situ hydrogen peroxide generator. Mechanistic similarities between the hydrocarbon oxidations observed here and those reported for direct addition of hydrogen peroxide demonstrate that the palladium does not participate in the substrate oxidation. More importantly, by using metallic palladium as a "hydrogen peroxide generator," *most* oxidation procedures that use hydrogen peroxide as the oxidant can, in principle, be converted to one that utilizes dioxygen. Of course, a coreductant, carbon monoxide or dihydrogen, will be required. However, from an economic standpoint,

hydrogen peroxide is significantly (five times) more expensive than either carbon monoxide or dihydrogen. This economic advantage is, of course, lost unless the oxidations can be made more efficient by minimizing the parallel palladium-catalyzed decomposition of hydrogen peroxide. The practical advantage of using an in situ hydrogen peroxide generator is that the transportation, storage and handling problems associated with hydrogen peroxide is eliminated, and the amount of water in the oxidation system is minimized.

## 5. Experimental

### 5.1. General procedures: caution

Due care must be taken when dealing with gas mixtures under pressure. Special attention must be paid to gas flammability limits [54].

All pressure reactions were performed in 300 ml Parr stainless steel autoclaves equipped with glass liners. Analyses were done on a HP-5890 series II

FID/TCD gas chromatograph with a 3396 Integrator. Quantitation was typically done using the FID detector excepting water quantitation reactions where the TCD detector was employed. Reactions with benzene used an Alltech EC-5 30 m, i.d. = 0.32 mm column with 100:1 split ratio and o-dichlorobenzene internal standard. Reactions of toluene were analyzed using a Supelco Nukol 30 m, i.d. = 0.25 mm column with a split ratio of 50:1 and 4-methyl benzyl alcohol internal standard. Cyclohexane and benzene quantitation reactions were analyzed with an Alltech EC-1000 30 m, i.d. = 0.25 mm column and utilized a 100:1 split ratio. m-Xylene and decane were used as an internal standard for the cyclohexane and benzene reactions, respectively. Analysis of gaseous products was done using a Supelco 15′ × 1/8″ 60/80 Carboxen 1000 packed column and referenced to nitrogen as an internal standard. Sampling of the reactions was performed by sending a portion of the headspace gas directly to the GC using an intermediate storage tank and a pneumatic gas sampling valve. Analyses involving isotope effects were performed at the Penn State MS facility on a HP-5972 with the columns listed above. Reaction products were confirmed using comparison to known compounds and further confirmed using GC-MS.

## 5.2. Materials

Ninety-five percent $^{18}$O-enriched water was purchased from Icon Isotope. $VO(O_2)(2\text{-picolinate})(H_2O)_2$ was synthesized according to literature methods [36]. All other materials were commercially available and used as received.

## 5.3. General reaction conditions

A total of 1.1 mg, 3.2 μmol of V(acac)$_3$ and 20.0 mg of 5% Pd on Al$_2$O$_3$ were weighed into ca. 25 ml constricted neck glass liner. To this a small magnetic stir bar was added along with 2 ml of benzene and 2.5 ml of glacial acetic acid. In the case of cyclohexane oxidation, cyclohexane (1.5 ml) and propionic acid (3 ml) were employed. The mixture was sealed in the autoclave and flushed thoroughly with dihydrogen. It was then charged with H$_2$ (100 psi), N$_2$ (1000 psi), and O$_2$ (100 psi) in that order and placed in a temperature regulated oil bath for 2 h. Internal autoclave temperatures were determined using an autoclave equipped with a temperature sensor. At the end of the reaction, the autoclave was cooled in ice, slowly degassed, and the contents filtered through a 2 μm filter to remove the supported palladium catalyst. After addition of internal standard, the liquid was analyzed by GC. Reactions were repeated and the results reported are the average of at least two experiments. When cyclohexane was the substrate, a 1 ml aliquot of the product mixture was removed after the internal standard had been added. A total of 52.6 mg, 0.200 mmol of triphenylphosphine was added to this aliquot and samples were analyzed via GC. Reactions of cyclopropyl derivatives were carried out using 1 ml of substrate and 3.5 ml of acetic acid. These reactions were analyzed using GC-MS.

Syringe pump reactions were carried out by weighing 1.1 mg, 3.2 μmol of V(acac)$_3$ into a 5 ml conical vial. Substrate and solvent were added so that the total volume after hydrogen peroxide addition was 4.5 ml. A solution of acetic acid or propionic acid (cyclohexane reactions) and 50% hydrogen peroxide (v/v, confirmed by permanganate titration) was made up to deliver 4.9 mmol of hydrogen peroxide in 0.68 ml of solution. This solution was delivered over a 2 h time period using a syringe pump and a 1 ml syringe constructed entirely of plastic and Teflon tubing (to prevent any premature peroxide decomposition). Reactions were chromatographed after internal standard addition. Reactions involving radical traps and nucleophiles were carried out similarly with the additional component added in at least 10-fold molar excess to substrate.

$^{18}$O enrichment experiments were carried out in a similar manner. For these reactions a 0.3 ml aliquot of water or 95% $^{18}$O-enriched water was added initially to the vial. Hydrogen peroxide was added using the anhydrous urea complex in a solution totaling 0.36 mmol of hydrogen peroxide in 0.68 ml of glacial acetic acid. Quantitation was done as described above. Isotopic enrichment was calculated by comparing the $m/z = 94/96$ ratio as compared to samples using $^{16}$O water.

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