Glycerol Oxidation

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Selective Catalytic Oxidation of Glycerol to Dihydroxyacetone**

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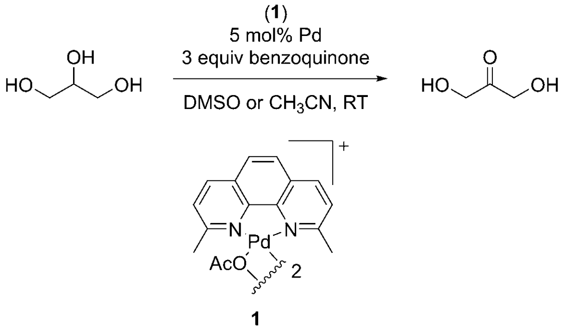
The increasing global demand for biodiesel has spawned an increase in the supply of glycerol.[1] Glycerol is an attractive and versatile feedstock as it is nontoxic, edible, and biodegradable, and it can be used as a building block for value-added chemicals.[1b,2] The development of novel, selective chemistry to provide new applications for glycerol-derived products remains a key challenge.[3]

Herein, we report the chemoselective, catalytic transformation of glycerol into dihydroxyacetone (Scheme 1). Dihydroxyacetone is produced on an industrial scale by the microbial oxidation of glycerol.[4] Recent advances in the catalytic oxidation of glycerol have generated a range of oxidation products,[3b,5] but few chemical catalysts are selective for dihydroxyacetone.[6] Palladium catalysts have been widely investigated for alcohol oxidation,[7] and exhibit modest chemoselectivities and similar rates for the oxidation of primary and secondary alcohols.[8] Previous reports on the catalytic oxidation of diols and polyols as substrates[8a,b,9] revealed higher chemoselectivities in some cases, prompting us to investigate whether the chemoselectivities observed for primary and secondary alcohols are different from that of diols. Herein, we describe the chemoselective catalytic oxidation of glycerol and 1,2-propanediol with palladium complex **1**[10] in the presence of either benzoquinone or air as a terminal oxidant. We show that these vicinal polyols exhibit both faster reaction rates and higher chemoselectivities than other primary and secondary alcohols, enabling the rapid chemoselective oxidation of glycerol into dihydroxyacetone under very mild conditions (RT, 1 atm air).



Scheme 1. Selective oxidation of glycerol to dihydroxyacetone.

The catalytic oxidation of glycerol with 5 mol% palladium (2.5 mol% **1**) and 3.0 equivalents of benzoquinone (BQ) in acetonitrile at room temperature proceeded with 97% conversion in 24 hours and >96% selectivity for dihydroxyacetone (Scheme 1, Table 1, entry 1). The nature of the solvent has a significant influence on the rate of reaction: in a 7:1 acetonitrile/water mixture (v/v), complete conversion of glycerol was observed in 3 hours.[11] When the reaction was conducted in dimethyl sulfoxide, the oxidation was complete within 15 minutes with complete selectivity for dihydroxyacetone. The selective oxidation of glycerol with **1** was readily performed on a 10 mmol scale in wet acetonitrile: oxidation of 0.92 g (10 mmol) of glycerol afforded dihydroxyacetone in 92% yield after chromatography, or 58% yield after crystallization of the product as its dimer (Table 1, entry 6).

Table 1: Catalytic oxidation of glycerol[a] and 1,2-propanediol (PG) with complex **1**.

Entry	Solvent	Diol	Ox.	*t* [h]	Conv. [%]	Sel. [%]	Yield [%]
1	CH_3CN	glycerol	BQ	24	97	99	
2	CH_3CN/H_2O[b]	glycerol	BQ	3	97	96	
3	DMSO	glycerol	BQ	0.25	97	99	
4	DMSO	PG	BQ	0.3	98	96	
5	DMSO	glycerol	air	24	47	80	
6	CH_3CN/H_2O[c]	glycerol	BQ	4	97		92
7	CH_3CN/H_2O[d]	glycerol	O_2	4	95		69
8	CH_3CN/H_2O[e]	glycerol	air	18			73

[a] Standard conditions: 0.1 mmol glycerol, 0.3 mmol BQ, 5 mol% Pd, 0.7 mL solvent, 23 °C. [b] CH_3CN/H_2O 7:1. [c] CH_3CN/H_2O 10:1, 10 mmol scale. [d] 10 mol% Pd, 1 atm O_2, CH_3CN/H_2O 10:1, 1 mmol scale. [e] 10 mol% Pd, sparged with air, 10:1 CH_3CN/H_2O, 10 mmol scale.

Significantly, the selective oxidation of glycerol can also be carried out aerobically. The oxidation of glycerol in wet acetonitrile under a balloon of O_2 with 10 mol% palladium (1 mmol scale) afforded the isolated dihydroxyacetone in 69% yield; on a larger scale (10 mmol glycerol), under a continuous stream of air, dihydroxyacetone was isolated in 73% yield after column chromatography on silica gel.

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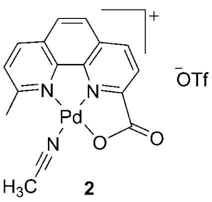
Attempts to perform the aerobic oxidation of glycerol at lower catalyst concentrations led to high selectivity for dihydroxyacetone, but low conversions: using 5 mol% palladium under a balloon of air afforded only 47% conversion after 24 hours in CD_3CN/D_2O. Competitive oxidative decomposition of the catalyst[10a] is a likely cause of the lower conversions and yields: the ^{1}H NMR spectrum of the final reaction mixture exhibited resonances characteristic of the palladium carboxylate (**2**) that we had previously shown to be inactive for alcohol oxidation.[10a] Thus, high conversions of glycerol into dihydroxyacetone can be achieved under aerobic conditions, but only at relatively high palladium concentrations.



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The oxidation of glycerol and 1,2-propanediol is faster and more selective than that of 1,3-diols or primary/secondary alcohols. Under similar conditions (5 mol% Pd, 3 equiv BQ, DMSO, 23 °C), oxidation of glycerol was complete within 15 minutes and oxidation of 1,2-propanediol to hydroxyacetone in dimethyl sulfoxide was complete within 20 minutes (Table 1). In contrast, the oxidation of a 1-heptanol/2-heptanol (1:1) mixture was both slower and nonselective, requiring 10 hours to reach 78% conversion and affording a 45:55 ratio of the ketone/aldehyde.[8a] Similarly, oxidation of 1,3-butanediol gave a 2:3 mixture of the ketone and aldehyde products in only 55% conversion after 4 hours.

The high chemoselectivity for the oxidation of the secondary alcohol of glycerol in the presence of two primary alcohols is noteworthy. Whilst many stoichiometric oxidants exhibit a preference for secondary over primary alcohols,[12] few chemoselective catalytic alcohol oxidations are known.[8,9b,13]

The lower rates and selectivities observed in the inter- and intramolecular competition experiments suggest that vicinal diols have an unusual reactivity with **1**. The kinetics of 1,2-propanediol oxidation with benzoquinone were monitored by ^{1}H NMR spectroscopy in dimethyl sulfoxide. With 1.5–3.0 equivalents of benzoquinone (relative to the diol), the disappearance of diol peaks conformed to a mixed-second-order kinetics analysis [Eq. (1)]:

$$\ln\left(\frac{[\mathrm{BQ}]_t}{[\mathrm{PG}]_t}\right) = \ln\left(\frac{[\mathrm{BQ}]_0}{[\mathrm{PG}]_0}\right) + k_{obs}([\mathrm{BQ}]_0 - [\mathrm{PG}]_0)t \qquad (1)$$

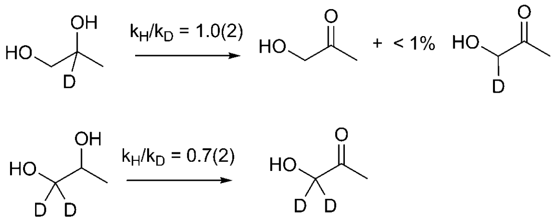
where [BQ] and [PG] are the concentrations of benzoquinone and 1,2-propanediol, respectively, and $t =$ time in seconds (see the Supporting Information). Plots of k_{obs} vs. [Pd] and the initial rates vs. [BQ] confirmed that the rates were first order in both [Pd] and [BQ] for $[\mathrm{BQ}] \leq 0.3\,\mathrm{M}$, thus yielding a rate law of [Eq. (2)]:

$$\mathrm{Rate} = k'[\mathrm{Pd}][\mathrm{PG}][\mathrm{BQ}] \qquad (2)$$

where $k_{\mathrm{obs}} = k'[\mathrm{Pd}]$ and $k' = 1.9(3)\,\mathrm{M}^{-2}\mathrm{s}^{-1}$ in [D_6]dimethyl sulfoxide at 23 °C.

In the presence of three equivalents of benzoquinone in either [D_3]acetonitrile or [D_6]dimethyl sulfoxide, the buildup of trace amounts of lactaldehyde ($< 5\%$) was observed during the course of the reaction, but disappeared after approximately 80% conversion. The relative concentration of lactaldehyde appeared to inversely correlate with the amount of water present in the reaction, as the highest amount of lactaldehyde (5% of the mass balance) was observed in dry acetonitrile.

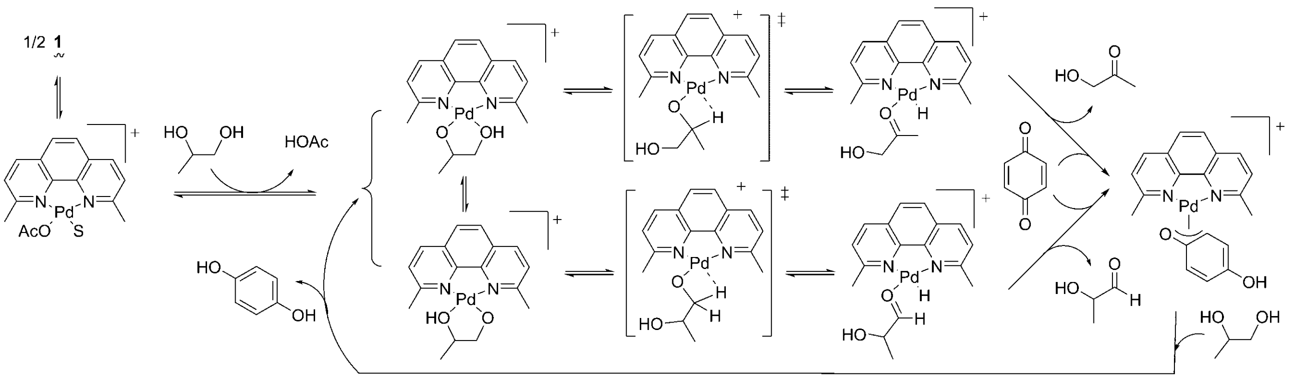
Whilst NMR studies indicated that lactaldehyde was formed during the course of the oxidation of 1,2-propanediol, deuterium-labeling studies suggested that the generation of a mixture of hydroxyacetone/lactaldehyde and subsequent isomerization of the aldehyde did not contribute significantly to the high selectivity for hydroxyacetone. Catalytic oxidation of [2-D]-1,2-propanediol with **1** in [D_6]dimethyl sulfoxide afforded unlabeled hydroxyacetone ($< 1\%$ deuterium-scrambling) and oxidation of [1,1-D_2]-1,2-propanediol gave [D_2]hydroxyacetone with 96% selectivity and 98% conversion. These experiments suggest that liberation of free lactaldehyde, followed by palladium- or acid-catalyzed tautomerization was not a major contributor to the high selectivity for hydroxyacetone. The second-order rate constants for the oxidation of [2-D]-1,2-propanediol and that for the undeuteriated diol are within experimental error ($k_{\mathrm{H}}/k_{\mathrm{D}} = 1.0(2)$), thus implying that β-H elimination was not rate-limiting.[8a,14] However, an inverse isotope effect of $k_{\mathrm{H}}/k_{\mathrm{D}} = 0.7(2)$ was evident from the ratio of rate constants for [1,1-D_2]-1,2-propanediol and 1,2-propanediol (Scheme 2).



Scheme 2. Oxidation of deuterium-labeled 1,2-propanediols.

On the basis of previous work,[7c,8a,10,14a] we propose that isomeric palladium alkoxides are formed by liberation of acetic acid from the cationic palladium acetate derived from dimeric **1**. β-H elimination from the alkoxides would generate a palladium hydride that reacts with benzoquinone to generate a cationic palladium/hydroquinone complex. Reaction of this hydroquinone complex with the diol regenerate the palladium alkoxide.

To investigate the role of the proton-transfer equilibria on the rate of reaction, we investigated the kinetics of 1,2-propanediol oxidation with benzoquinone in the presence of 5, 10, and 20 mol% acetic acid (HOAc, relative to the diol) and found that the rates were inverse first order in [HOAc] ($k' = k''/[\mathrm{HOAc}]$). This observation is consistent with the reversible generation of the alkoxide from the reaction of the cationic palladium acetate (Scheme 3). The first-order dependence on benzoquinone implies that re-oxidation of palladium(0) or the Pd-H[15] species is rate-limiting in



Scheme 3. Proposed mechanism for the catalytic oxidation of 1,2-propanediol. S = solvent.

dimethyl sulfoxide (Scheme 3). This dependence is unusual for palladium-mediated alcohol oxidation, but is consistent with the absence of a primary kinetic isotope effect. The origin of the inverse secondary isotope effect[16] is not clear at present.

The higher selectivities observed for the oxidation of glycerol/1,2-propanediol relative to 1- and 2-heptanol implies that the product-determining steps for the intra- and intermolecular oxidations are different. One possibility is that β-H elimination is not the sole product-determining step,[17] but that both the reversible formation of the palladium alkoxides and β-H elimination contributes to the selectivities. Alternatively, if the β-H elimination was reversible, selective displacement of the bound ketone from the Pd–H intermediate could explain the high selectivity for hydroxyketone formation. Further kinetic and mechanistic studies are underway to test these hypotheses.

In summary, glycerol is selectively and rapidly oxidized into dihydroxyacetone with the cationic palladium catalyst **1** using benzoquinone or oxygen as the terminal oxidant. Vicinal diols appear to be privileged substrates for this catalyst system, and are oxidized with high rates and selectivities into hydroxyketones. Studies to explore the mechanism and scope of the oxidation of polyols are currently underway.

Experimental Section

Table 1, entry 5: Glycerol (0.92 g, 10 mmol) and benzoquinone (3.24 g, 30 mmol) were dissolved in a mixture of 30 mL CH_3CN and 3 mL H_2O. Catalyst **1** (260 mg, 0.25 mmol) was then added to the solution, thus resulting in a reddish-brown solution. The solution was stirred at RT until complete consumption of glycerol was evident by TLC. The solution was then poured into 300 mL diethyl ether to precipitate out the catalyst and then filtered through a plug of silica gel (60 g), eluting with diethyl ether, and collected in 30 mL fractions until the eluent was colorless. The dihydroxyacetone was purified by column chromatography on silica gel using acetone to yield 0.83 g of dihydroxyacetone as a colorless and extremely hygroscopic oil (92 %).

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