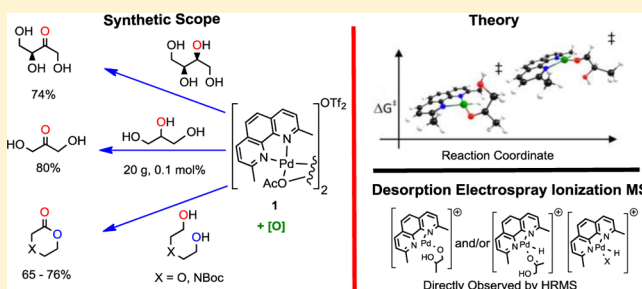# Chemoselective Pd-Catalyzed Oxidation of Polyols: Synthetic Scope and Mechanistic Studies

Kevin Chung,[†] Steven M. Banik,[†] Antonio G. De Crisci, David M. Pearson, Timothy R. Blake, Johan V. Olsson, Andrew J. Ingram, Richard N. Zare, and Robert M. Waymouth*

Department of Chemistry, Stanford University, Stanford, California 94306, United States

S *Supporting Information*

ABSTRACT: The regio- and chemoselective oxidation of unprotected vicinal polyols with [(neocuproine)Pd-(OAc)]₂(OTf)₂ (**1**) (neocuproine = 2,9-dimethyl-1,10-phenanthroline) occurs readily under mild reaction conditions to generate α-hydroxy ketones. The oxidation of vicinal diols is both faster and more selective than the oxidation of primary and secondary alcohols; vicinal 1,2-diols are oxidized selectively to hydroxy ketones, whereas primary alcohols are oxidized in preference to secondary alcohols. Oxidative lactonization of 1,5-diols yields cyclic lactones. Catalyst loadings as low as 0.12 mol % in oxidation reactions on a 10 g scale can be used. The exquisite selectivity of this catalyst system is evident in the chemoselective and stereospecific oxidation of the polyol (*S,S*)-1,2,3,4-tetrahydroxybutane [(*S,S*)-threitol] to (*S*)-erythrulose. Mechanistic, kinetic, and theoretical studies revealed that the rate laws for the oxidation of primary and secondary alcohols differ from those of diols. Density functional theory calculations support the conclusion that β-hydride elimination to give hydroxy ketones is product-determining for the oxidation of vicinal diols, whereas for primary and secondary alcohols, pre-equilibria favoring primary alkoxides are product-determining. In situ desorption electrospray ionization mass spectrometry (DESI-MS) revealed several key intermediates in the proposed catalytic cycle.

INTRODUCTION

Selective catalytic oxidation reactions are among the most useful and challenging synthetic transformations.[1−8] The chemoselective oxidation of polyols[9−14] provides a powerful strategy for the synthesis of α-hydroxy ketones, a recurring motif in natural products and a versatile class of synthetic intermediates.[15−21] The oxidation of vicinal diols is particularly challenging because of competitive C−C cleavage reactions, overoxidation, or poor chemoselectivity.[4,22] Recent advances include methods with stoichiometric dioxiranes,[23] tin oxides,[10] catalytic RuCl₃ in carefully buffered oxone,[19,24,25] and electrocatalysis.[26]

Palladium complexes are versatile alcohol oxidation catalysts,[2,3,27−30] particularly for aerobic oxidations under mild conditions.[3,11,31−38] While homogeneous Pd catalysts typically exhibit modest selectivities for the oxidation of secondary over primary alcohols,[28,33,36,39] recent studies have revealed that high chemoselectivities can be achieved in the oxidation of diols[11,12,40] and triols.[9] We recently described the selective catalytic oxidation of glycerol to dihydroxyacetone by the cationic palladium complex [(neocuproine)Pd(OAc)]₂[OTf]₂ (**1**) (neocuproine = 2,9-dimethyl-1,10-phenanthroline).[9] The cationic palladium complex **1** is active at ambient temperature for the selective oxidation of vicinal 1,2-diols to hydroxy ketones, whereas the oxidation of primary and secondary aliphatic alcohols is less selective, favoring oxidation of the primary alcohol.[9,41−43] Dioxygen, air, and benzoquinone (BQ) can be used as terminal oxidants;[9,41−43] aerobic oxidations are most convenient, but aerobic oxidations with **1** require Pd loadings of approximately 10 mol % because of competitive oxidative degradation of the neocuproine ligand.[9,41,43]

Herein we describe the chemoselective oxidation of a variety of unprotected polyols to hydroxy ketones and the oxidative lactonization of 1,5-diols to cyclic lactones. When BQ is used as the terminal oxidant, the catalyst loading can be as low as 0.12 mol % on a 10 g scale. Kinetic and mechanistic investigations coupled with density functional theory (DFT) calculations provided insights into the origin of both the high selectivities and higher rates of oxidation of vicinal diols relative to primary and secondary alcohols. In operando desorption electrospray ionization mass spectrometry (DESI-MS) of reaction mixtures with Pd catalyst **1** and 1,2-propanediol revealed ions that correspond to several key intermediates in the proposed catalytic cycle.
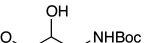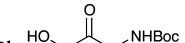
SYNTHETIC SCOPE

A variety of diols and polyols were oxidized with **1** to afford the corresponding hydroxy ketones using BQ, O₂, or air as the oxidant in 9:1 (v/v) CD₃CN/D₂O (Table 1). High selectivities

Table 1. Chemoselective Oxidation of Polyols with [(neocuproine)Pd(OAc)]$_2$(OTf)$_2$ (1)

Entry	ROH/Pd mmol	Substrate	Major product	t, [T] (h,°C)	Oxid.	Conv.[a] (%)	Yield[b] (%)	Sel.[c] (%)
1	0.1/0.010	2	2b	2[25]	BQ[d]	95		99
2	1/0.10	3	3b	20[25]	BQ[e]		88	
3	0.1/0.005	4	4b	3[25]	BQ[d]	97		99[f]
4	118/0.136			72[70]	BQ[e]		65	
5	0.1/0.005	5	5b	2[25]	BQ[d]	62		
6	10/0.10			20[25]	O$_2$		71	99
7	10/0.012			48[70]	BQ[e]		62	
8	0.1/0.010	6	6b	2[25]	BQ[d]	99		72
9	11/1.1			24[25]	Air		74	
10	1/0.10	(S,S)-7	(S)-7b	20[25]	O$_2$		86	(98% ee)[h]
11	1.15/0.10	(R,R)-7	(R)-7b	20[25]	O$_2$		87	(97% ee)[h]
12	0.1/0.010	8	8b	2[25]	BQ[d]	57		66
13	10.16/2.08	9	9b	72[60]	O$_2$	99	76	
14	21.1/2.38	10	10b	48[60]	O$_2$	99	65	
15	0.1/0.010	11-cis	11b	2[25]	BQ[d]	94		99
16	10/1.0			8[25]	O$_2$		81[f]	
17	10/1.0	11-trans	11b	3[25]	O$_2$		81	
18	10/1.08			8[25]	Air		74	
19	0.33/.032	12	12b	8[25]	O$_2$	99	83	90
20	0.34/.032	13	13b	8[25]	O$_2$	75	60	85
21	0.35/0.034	14	14b	11[25]	O$_2$	70	65[g]	50

All of the reactions were conducted in a 9:1 (v/v) CH$_3$CN/H$_2$O solvent mixture. [a]Determined by ^{1}H NMR integration vs p-xylene as an internal standard. [b]Isolated yields. [c]Selectivities determined by ^{1}H NMR integration of major product/conversion. [d]3 equiv of BQ relative to ROH. [e]See the Supporting Information for the amount of BQ. [f]Exclusively dimer. [g]Combined yield of the two regioisomers, which were formed in a 1:1 ratio. [h]Determined by chiral HPLC on the trisacetylated product (see the Supporting Information for details).

for the formation of hydroxy ketones in the oxidations of diols 2−14 were observed,[44] although more highly activated alcohols such as 2-hydroxy-1-indanol underwent competitive over-oxidation to give the 1,2-diketone. This selectivity implies that hydroxy ketones are oxidized much more slowly than the diols. Oxidations catalyzed by 1 are tolerant of N-tert-butoxycarbonyl (N-Boc)-protected amines: N-Boc-protected aminodiol 3 reacted cleanly to form α-hydroxy ketone 3b in 88% yield (entry 2; also see entry 13).
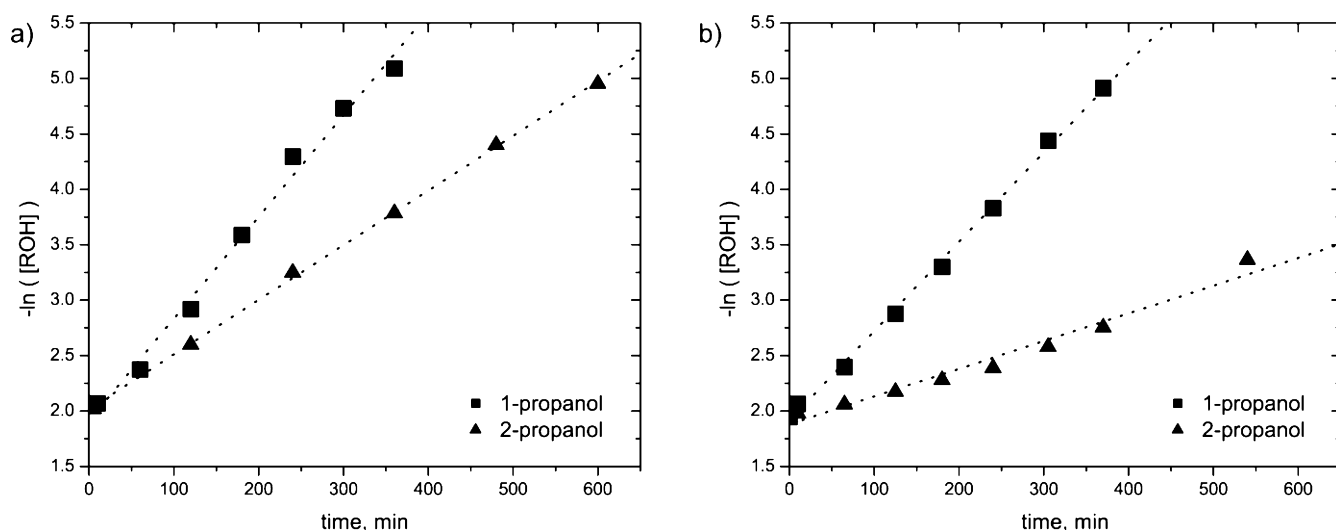
Figure 1. First-order plots for oxidations of mono-ols measured (a) independently ([Pd] = 0.0143 M, [ROH]$_0$ = 0.143 M) and (b) in a competition experiment (1-propanol/2-propanol =1:1, [ROH]$_T$ = 0.143 M, [Pd] = 0.0143 M) using 10 mol % Pd catalyst **1** with 2 equiv of BQ relative to mono-ol in 9:1 (v/v) CD$_3$CN/D$_2$O.

NMR investigations revealed that the catalytic oxidation of 1,2,4-butanetriol (**5**) was more selective (99% vs 66%) than the oxidation of 1,3,5-pentanetriol (**8**) to yield hydroxy ketones **5b** and **8b**, respectively. The oxidation of the triols glycerol (**4**) and **5**[45] with BQ could be carried out with Pd loadings as low as 0.12 mol %, providing dihydroxyacetone and 1,4-dihyroxybutanone in isolated yields of 64% and 62%, respectively; in the case of glycerol, this was carried out on a 10 g scale. Similar high chemoselectivities have been reported in stoichiometric or electrocatalytic oxidations of diols with Pt/C/Bi$_2$O$_3$,[26] Bu$_2$Sn=O,[10] or Me$_2$SnCl$_2$;[10] the utility of these methods was highlighted in the synthesis of spectinomycin[17] and in carbohydrate synthesis.[46,47] As the latter methods require the synthesis of stannylene acetals, the atom economy and operational simplicity of the Pd-catalyzed aerobic oxidations constitute a particular advantage over these powerful methods.

The chemoselective and stereospecific oxidations of the tetraols erythritol (**6**) and threitol (**7**) are noteworthy; these tetraols were oxidized selectively to the hydroxy ketone erythrulose in isolated yields of 65−87%. The oxidations of optically active (*S,S*)- and (*R,R*)-threitol were stereospecific, affording (*S*)- and (*R*)-erythrulose with greater than 97% retention of configuration. These latter results imply that under these conditions, racemization due to enolization is minimal.[9] While the enzymatic or microbial oxidation of erythritol is known,[48] the chemoselective catalytic oxidation of erythritol by **1** represents an attractive strategy for the selective oxidation of unprotected polyols. Furthermore, the generation of highly enantiomerically pure erythruloses from the threitol enantiomers (*S,S*)-**7** and (*R,R*)-**7** highlights the advantages of the slightly acidic conditions used with complex **1** (CH$_3$CN/H$_2$O) for the generation of base-sensitive optically active hydroxy ketones.

The catalytic oxidative lactonization of α,ω-diols is a useful strategy for generating lactones.[38,49−54] The oxidative lactonization of diethylene glycol (**10**) with a heterogeneous Cu/Zn catalyst at 350 °C in a flow reactor generated the cyclic lactone *p*-dioxanone (**10b**), as previously reported in the patent literature.[53,55] More recently, Milstein developed a milder oxidative lactonization (115 °C, 48 h) of 1,5-pentanediols with Ru pincer complexes.[52] The aerobic oxidation[38] of **10** on a 2 g scale afforded a 65% isolated yield of **10b**. Oxidative lactonization by **1** likely occurs by initial oxidation to give the hydroxy aldehyde followed by cyclization and subsequent oxidation of the lactol[49] in a manner similar to that proposed for the oxidation of methanol with **1** to give methyl formate.[42] Oxidative lactonization of *N*-Boc-protected aminodiol **9** afforded a 76% yield of the corresponding lactone **9b**.

Internal vicinal diols **11−14** were also oxidized selectively to the corresponding hydroxy ketones **11b−14b**. The aerobic oxidations of *trans*-1,2-cyclohexanediol (**11-trans**) and **6** afforded similar yields when O$_2$ or air was used as the oxidant. Reactions catalyzed by Pd catalyst **1** exhibited a preference for oxidation of the axial hydroxyl group in the diastereomerically defined cyclohexane diols **12** and **13**.[10] In contrast, the diaxial diol **14** afforded a 1:1 mixture of the isomeric hydroxy ketones **14b**. These results indicate that for substrates containing both axial and equatorial hydroxyls, the axial hydroxyls are oxidized preferentially; nevertheless, diequatorial diols are competent substrates, as **11-trans**[56] was readily oxidized to yield 2-hydroxycyclohexanone.

Mechanistic investigations were carried out to illuminate the origin of the higher rates and selectivities observed for oxidation of diols and polyols relative to primary or secondary alcohols. We had previously shown that **1** is capable of oxidizing 1-heptanol to heptanal and 2-heptanol to 2-heptanone.[43] To assess the origin of the selectivity of oxidations of primary and secondary alcohols catalyzed by **1**, the oxidations of 1-propanol and 2-propanol were investigated in dry acetonitrile. Kinetic experiments revealed that 1-propanol is oxidized to propanal more rapidly than 2-propanol is oxidized to acetone by a factor of 1.8:1, whereas competitive oxidation of a 1:1 mixture of the isomeric propanols exhibited a slightly higher preference for oxidation of the primary alcohol, yielding a mixture of the aldehyde and the ketone in a ratio of 3.2:1 (Figure 1).[57]

Despite the preference for primary alcohols in intermolecular competition experiments, oxidation of the vicinal 1,2-diols in Table 1 exhibited an enhanced selectivity for the oxidation of
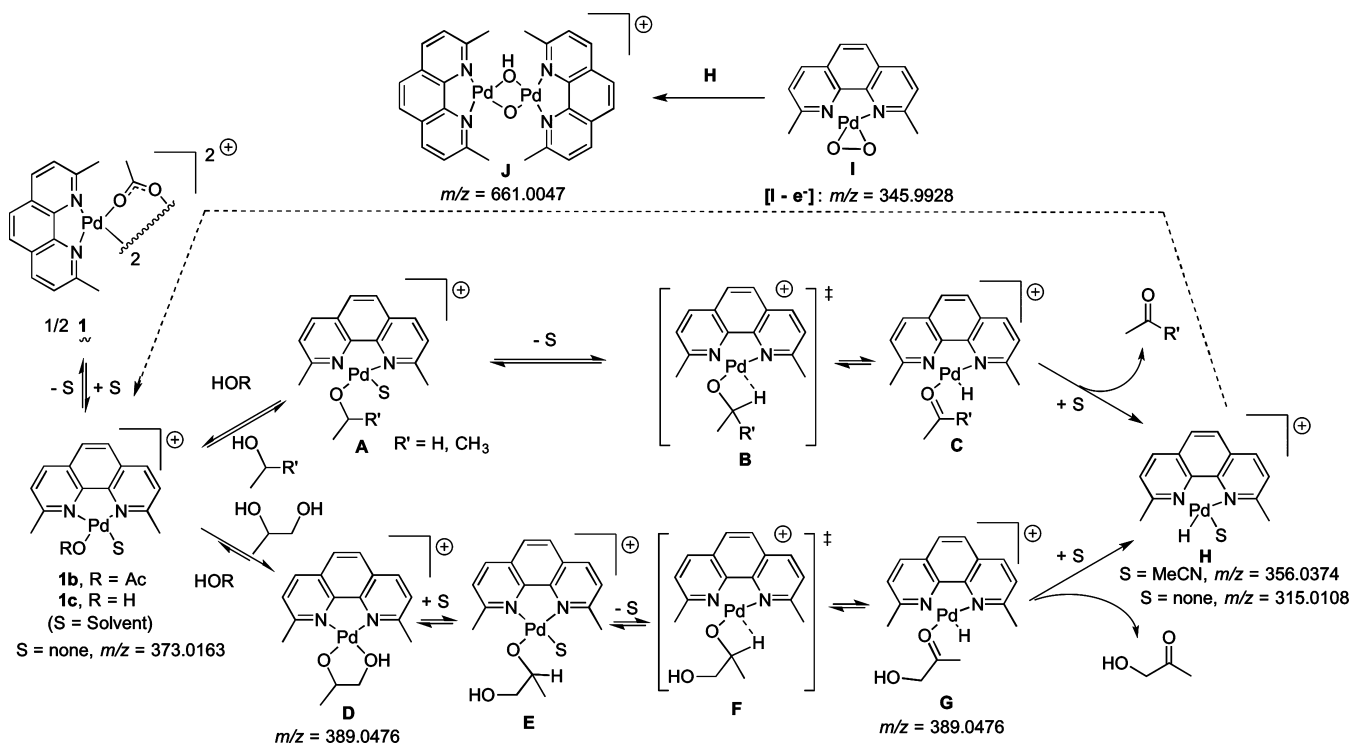
Figure 2. Proposed mechanism and observed intermediates for oxidation of (upper path) primary or secondary alcohols and (lower path) vicinal diols. Species observed by DESI-MS are labeled with their theoretical m/z values. The transformation of **H** to **1b** or **1c** can occur using benzoquinone or O_2; proposed intermediates for the case of oxidation with O_2 are shown along the dotted line.

the secondary alcohol to generate the α-hydroxy ketone.[9] This reversal in chemoselectivity for vicinal 1,2-diols relative to that for primary and secondary alcohols suggests that the product-determining step for oxidation of vicinal diols is different than that for primary and secondary mono-ols.

The higher chemoselectivity exhibited by **1** for the oxidation of diols relative to mono-ols is also manifested in their kinetic behavior. We previously showed that the oxidation of 1,2-propanediol (**2**) to hydroxyacetone (**2b**) in dimethyl sulfoxide (DMSO) is very fast and conforms to the rate law[9]

$$-\frac{d[\mathbf{2}]}{dt}\bigg|_{DMSO} = k_1[\text{Pd}][\mathbf{2}][\text{BQ}] \tag{1}$$

where $k_1 = 1.9(3)\ \text{M}^{-2}\ \text{s}^{-1}$. While the solvent has little influence on the chemoselectivity, it has a dramatic influence on the rate: the oxidation of **2** to **2b** with BQ in dry CD_3CN is slower than in DMSO and is zeroth order in diol and BQ (Figure S3 in the Supporting Information):

$$-\frac{d[\mathbf{2}]}{dt}\bigg|_{CD_3CN} = k_2[\text{Pd}] \tag{2}$$

where $k_2 = 4.6 \times 10^{-2}\ \text{s}^{-1}$. The insensitivity of the rate to the alcohol concentration in dry CD_3CN is also manifested in the lack of a kinetic isotope effect: comparison of the rate constants for oxidation of 1,2-propanediol and 1,2-propanediol-2-d in CD_3CN yielded $k_2^H/k_2^D = 1.03$.

In contrast, the oxidations of 1-propanol and 2-propanol in dry CD_3CN are both slower than that of 1,2-propanediol and are first order in alcohol under similar conditions (Figure S5 in the Supporting Information):

$$-\frac{d[\text{1-propanol}]}{dt}\bigg|_{CD_3CN} = k_3[\text{Pd}][\text{1-propanol}]$$

$$-\frac{d[\text{2-propanol}]}{dt}\bigg|_{CD_3CN} = k_4[\text{Pd}][\text{2-propanol}] \tag{3}$$

where $k_3 = 10.7 \times 10^{-3}\ \text{M}^{-1}\ \text{s}^{-1}$ and $k_4 = 5.7 \times 10^{-3}\ \text{M}^{-1}\ \text{s}^{-1}$. In contrast to the case for 1,2-propanediol, a kinetic isotope effect of $k^H/k^D = 1.5$ was determined for 2-propanol from the ratio of the pseudo-first-order rate constants for 2-propanol and 2-propanol-2-d.[28,29,58,59] Moreover, when the rates of oxidation were measured in a competition experiment using a 1:1 mixture of 1-propanol and 2-propanol, the rate constant for 1-propanol oxidation ($k_3' = 9.4 \times 10^{-3}\ \text{M}^{-1}\ \text{s}^{-1}$) was similar to that observed in the absence of 2-propanol, but the rate constant for 2-propanol oxidation ($k_4' = 2.9 \times 10^{-3}\ \text{M}^{-1}\ \text{s}^{-1}$) was lower than that observed in the absence of 1-propanol (Figure 1). Thus, in the presence of 1-propanol, the rate of 2-propanol oxidation in CD_3CN decreases by a factor of 1.9, whereas the rate of 1-propanol oxidation is only moderately influenced by the presence of 2-propanol. These observations indicate that 1-propanol acts as a competitive inhibitor of 2-propanol, which can explain the higher selectivity for the competition experiment ($k_{prim}/k_{sec} = 3.2$) relative to that measured from the relative rates in separate experiments ($k_{prim}/k_{sec} = 1.9$).

Water has a differential effect on the rates of diol versus mono-ol oxidation. Added water increases the rate of 1,2-propanediol oxidation but inhibits 2-propanol oxidation in CD_3CN. Addition of D_2O to CD_3CN (1:9 mixture) increases the rate and changes the rate law in such a way that 1,2-propanediol oxidation becomes first order in diol (Figure S4 in the Supporting Information). The influence of D_2O on the rate

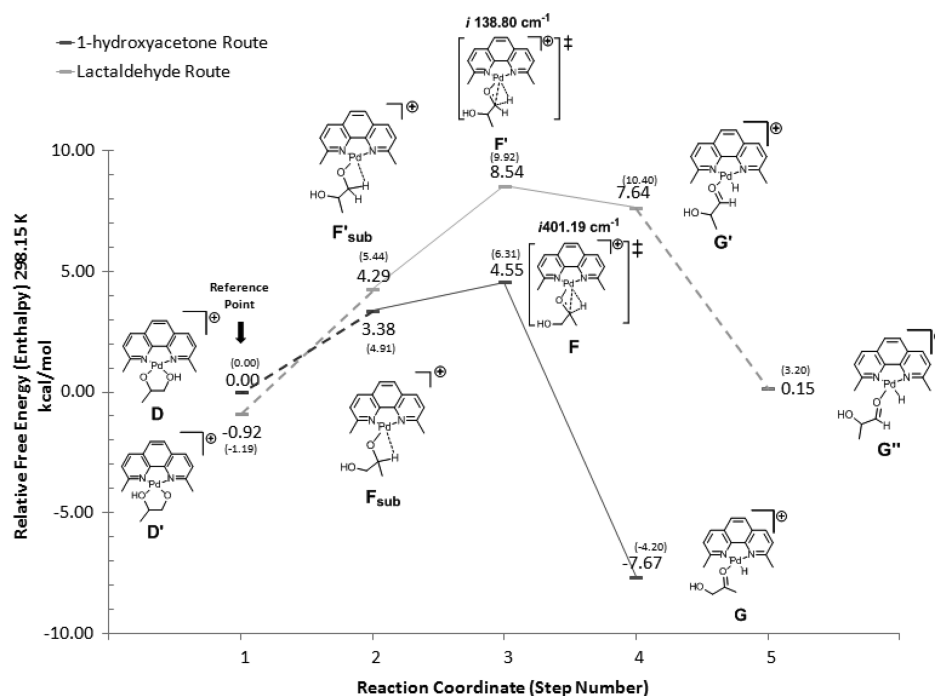**Figure 3.** DFT-computed reaction coordinate using Gaussian 09 at the M06L/6-311G(d,p)/SDD(f) level. Values of free energy (enthalpy) in kcal/mol at 298.15 K are shown. All of the calculations were done in the gas phase. Structures F_{sub}, F'_{sub}, G, and G' were found to be connected by IRC analysis and are joined by solid lines. Dashed lines connect structures that were not connected by IRC analysis but exist on the potential energy surface. All of the structures were confirmed by vibrational analysis. An electronic energy plot (Figure S12) and a solvent-phase plot (CPCM model, MeCN solvent; Figure S14) are shown in the Supporting Information.

of 1,2-propanediol oxidation in dry CD_3CN is mirrored in the effect with added DMSO (Figure S7 in the Supporting Information); the rate of 1,2-propanediol oxidation also increases with increasing [DMSO] up to [DMSO] ≈ 0.4 M, above which the reaction becomes first order in 1,2-propanediol.

Shown in Figure 2 is a proposed mechanism for the catalytic oxidation of alcohols and vicinal diols. Previous studies[9,41] had indicated that the acetate-bridged dimer **1** dissociates in MeCN, water, or DMSO to give the monomeric species **1b**[41] and/or **1c**.[28] Upon addition of alcohol, ligand exchange would generate hydroxyalkoxide chelate **D** derived from a vicinal diol or alkoxide **A** derived from a primary or secondary alcohol. Subsequent β-H elimination from cationic diolate **D** would form palladium hydride **G**. Release of the hydroxy ketone from **G** via solvent substitution would form **H**, which would be oxidized by BQ or O_2 to reform **1b** or **1c**. In the case of monool oxidation, alkoxide intermediate **A** would undergo β-H elimination to form the ketone- or aldehyde-coordinated complex **C**, and subsequently the Pd hydride **H**.

The kinetic studies of the isomeric propanols imply that in acetonitrile, equilibration between **1b** and Pd alkoxide **A** is both rate- and product-determining for the oxidation of primary and secondary alcohols. This is supported by the inhibition of 2-propanol oxidation in the presence of 1-propanol, D_2O (10% relative to CD_3CN), HOAc (0.5 equiv relative to **1**), or propanal (Figure S6 in the Supporting Information). The inhibition of 2-propanol oxidation by 1-propanol suggests that the equilibria to form Pd alkoxides **A** are biased to form the primary alkoxide. This hypothesis can also explain the chemoselectivity favoring oxidation of the primary alcohol: in this case, the chemoselectivity for oxidation of primary and secondary alcohols can be ascribed to product-determining pre-

equilibria favoring the primary alkoxide followed by β-H elimination.

In contrast, the oxidation of 1,2-propanediol is zeroth order in diol in dry CD_3CN, indicating that hydroxyalkoxide chelate **D** is a resting state in dry CD_3CN. The higher rates of 1,2-propanediol oxidation relative to the isomeric propanols is likely a consequence of a more favorable ligand-exchange equilibrium to generate chelating protonated diolate **D** from **1a/1b**. The origin of the accelerating influence of added water or DMSO on the rate of diol oxidation is not clear; one possibility is that reversible coordination of DMSO or water to chelate **D** facilitates the isomerization of **D** to the agostic alkoxide **F**, which could then undergo β-H elimination.

For 1,2-propanediols, we propose that β-H elimination is product-determining. If β-H elimination were faster for secondary alcohols relative to primary alcohols, then the high chemoselectivity for the formation of α-hydroxy ketones from 1,2-diols could be attributed to a product-determining intramolecular selectivity for β-H elimination from the secondary alkoxide. As there are few mechanistic or theoretical studies that address the relative barriers for β-H elimination from primary and secondary Pd alkoxides, DFT studies were carried out to assess the relative barriers for β-H elimination from diols and primary or secondary alcohols.

■ THEORETICAL STUDIES

DFT calculations were carried out using the Gaussian 09 software package[60] at the M06L[61]/SDD(f)/6-311G(d,p) level of theory [the M06L functional, the triple-ζ polarized 6-311G(d,p) basis set[62] for light atoms, and the SDD[63] effective core potential for Pd with augmented f orbitals[64]] with default convergence criteria in the gas phase. The gas-phase harmonic vibrational frequencies were used for the thermal and entropic

corrections to the enthalpies and free energies using default parameters at 298.15 K.

The DFT-computed reaction coordinate involving 1,2-propanediol oxidation is shown in Figure 3 using the free energies and enthalpies at 298 K in the gas phase (see Computational Details in the Supporting Information for details).[65] For these studies, hydroxyalkoxide complex **D** was chosen as the reference point; its tautomer **D′** is slightly lower in energy (Figure 3). The O−Pd−O bite angles in **D** and **D′** are similar at 79.6 and 81.7° respectively, signifying only slight changes in the palladium's coordination geometry; both structures exhibit a slightly distorted square-planar geometry.

β-Hydride elimination is initiated by isomerization of **D** and **D′** to the agostic[66] alkoxides **F**$_{sub}$ and **F′**$_{sub}$, respectively, which are characterized by three-center−two-electron interactions with the β-hydrogen. These local minima were located on the intrinsic reaction coordinate (IRC) from the transition states and exhibit Pd−H bond distances of 1.80 and 1.84 Å and Pd−H−C bond angles of 100 and 98° for **F**$_{sub}$ and **F′**$_{sub}$, respectively; both have elongated C−H distances of ∼1.21 Å. These structures are 3.38 and 5.21 kcal/mol higher in free energy relative to the hydroxyalkoxides **D** and **D′**, respectively.

Two transition states for β-hydride elimination (**F** and **F′**) were located, and IRC analysis was performed on either side of the transition states. The Pd−H (1.59 and 1.57 Å), Pd−O (2.07 and 2.10 Å), and Pd−C (2.38 and 2.34 Å) bond distances for transition states **F** and **F′**, respectively, were similar to one another and to those calculated previously for related Pd systems.[58,59,67−69] The DFT-computed barrier for β-H elimination for the secondary alkoxide ($\Delta G^{\ddagger} = +4.55$ kcal/mol) is lower than that of the primary alkoxide ($\Delta G^{\ddagger} = +9.46$ kcal/mol) by 4.91 kcal/mol. These calculation suggest that β-H elimination from protonated diolate **D** should favor the hydroxy ketone, as observed experimentally.

The IRC analysis revealed that the free energy of η^1-hydroxy ketone adduct **G** (Pd−O = 2.14 Å, Pd−H = 1.54 Å) is lower than that of the hydroxy aldehyde adduct **G″** (Pd−O = 2.15 Å, Pd−H = 1.54 Å) by 7.8 kcal/mol. The IRC calculations revealed another local minimum, **G′**,[70] very near the transition state **F′** for lactaldehyde formation. To first order, this suggests that the greater thermodynamic stability of ketones (relative to aldehydes) is partially manifested in the transition states, favoring the ketone product. The calculated geometries of the transition states **F** and **F′** imply that there may be a steric component as well: the calculated Pd−O−C−H dihedral angle for transition state **F′** (yielding the aldehyde) is 14.8°, whereas that for transition state **F** (yielding the ketone) is −6.2°. These data suggest that the steric demands of the methyl substituents at the 2 and 9 positions of the neocuproine ligand may also differentially bias the transition states in favor of the ketone product. Theofanis and Goddard[71] and others[72−74] have proposed that β-hydride elimination is most facile when the moiety formed by the Pd, α, β, and H atoms (i.e., the Pd−O−C−H moiety in this case) is planar.

Similar structural parameters were observed for the η^1-ketone adduct **G**. Notably, the relatively short C−O distances observed in both the transition states for β-H elimination (1.28 and 1.26 Å for **F** and **F′**, respectively) and the cationic Pd−H carbonyl adducts **G**, **G′**, and **G″** (1.23, 1.24, and 1.22 Å, respectively) imply that for these Pd systems, β-H elimination generates η^1-bound aldehyde or ketone adducts with minimal back-bonding from Pd into the incipient carbonyl adducts.[58,67]

We also computed the relative barriers for β-H elimination from the cationic [(neocuproine)PdOR]$^+$ alkoxides derived from 1-propanol and 2-propanol (see Figure S15 in Supporting Information for details). These calculations revealed lower barriers for β-H elimination from the secondary Pd isopropoxide relative to the primary Pd alkoxide derived from 1-propanol ($\Delta\Delta G^{\ddagger} = 6.94$ kcal from the agostic alkoxide intermediates). In addition, the η^1-acetone adduct of the cationic Pd−H was 11.25 kcal/mol lower in free energy than the corresponding η^1-propanal adduct.

The DFT calculations imply that for the cationic Pd−neocuproine system derived from **1**, β-H elimination is more favorable from secondary alkoxides than from primary alkoxides. These results would suggest that under conditions where β-H elimination is product-determining, the ketone should be favored relative to the aldehyde. This behavior is in contrast to that predicted by DFT calculations on β-H elimination at electron-rich Ir(I)[75] and Ru(II)[76] centers. For Ru(II) phosphine complexes, DFT calculations indicated that the product carbonyls are strongly η^2-bound and that there is little difference in the calculated barriers for β-H elimination for primary (methoxide) versus secondary (isopropoxide) alkoxides.[76] In kinetic studies of d^8 Ir(I) complexes, Hartwig and co-workers[72] observed little difference in rate for β-H elimination from primary or secondary Ir(I) alkoxides. These data suggest that the nature of both the metal and ligand environments can have a significant influence on the relative rates of β-H elimination of metal alkoxides.

■ DIRECT OBSERVATION OF INTERMEDIATES BY DESI-MS

To provide further evidence for the intermediates proposed in Figure 2, DESI-MS[77,78] studies were undertaken to identify species present during the reaction. Electrospray ionization mass spectrometry (ESI-MS) has proven useful for identifying reactive intermediates in other Pd-catalyzed reactions;[79] here we show that DESI-MS is particularly useful for aerobic oxidation reactions. In this application of DESI-MS, charged primary microdroplets from an electrospray source containing CH$_3$CN solvent or 1,2-propanediol in CH$_3$CN were bombarded on a surface containing Pd complex **1**. The secondary microdroplets emanated from the surface were directed toward the inlet of a mass spectrometer for detection of the ionic species formed on the surface or inside the secondary microdroplets (Figure S8 in the Supporting Information).[80,81] This technique was recently used to perform millisecond[82−84] and submillisecond[85] time scale investigations of organometallic reactions as well as to intercept intermediates with fleeting lifetimes[86] and provides a complementary approach to conventional ESI-MS techniques[82] for the study of reaction intermediates.

The DESI-MS spectrum of pure **1** was taken using procedures described previously,[82,83] wherein 10 μL of a 0.01 M solution of **1** in CH$_3$CN was deposited on paper affixed to a glass slide and pure CH$_3$CN was sprayed onto the surface using a custom DESI source held at 5 kV (Figure S9 in the Supporting Information). High-resolution MS data were gathered on an Orbitrap mass spectrometer;[87,88] collision-induced dissociation (CID) studies, a version of tandem mass spectrometry (MS/MS), were performed on a low-resolution quadrupole ion trap instrument. Peaks corresponding to Pd species were easily identified by the characteristic isotope pattern of Pd, and molecular formulas were assigned by

[1b − S]⁺
m/z = 373.0163

[(1b-S)₂(OTf)]⁺
m/z = 896.9864

[(1c − S)₂(OTf)]⁺
m/z = 812.9648

[J]⁺
m/z = 663.00463

[(I - e⁻)]⁺
m/z = 345.9930

[(I - e⁻) - O₂]⁺
m/z = 314.0031
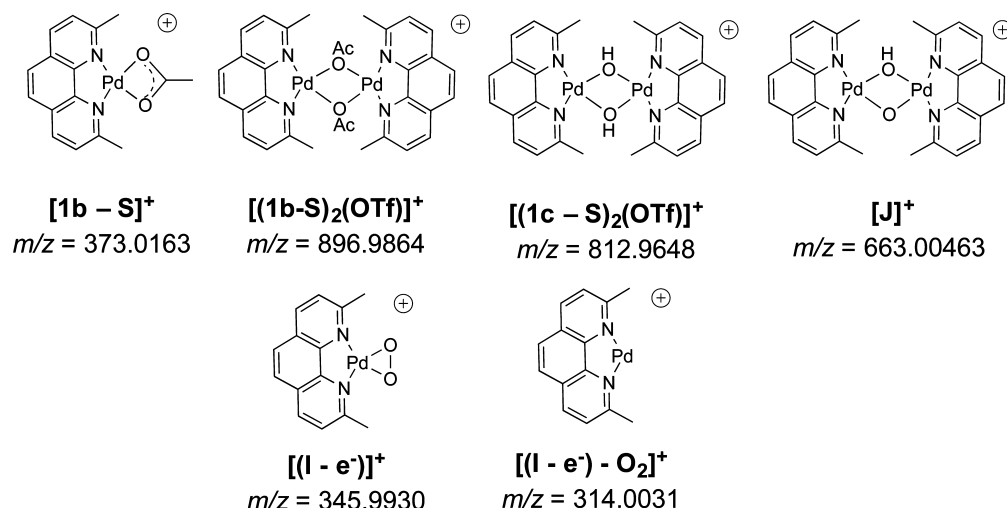
Figure 4. Representative ions observed by DESI-MS of [(L)Pd(OAc)]₂(OTf)₂ (**1**).

[D]⁺
m/z = 389.0477

and/or

[G]⁺
m/z = 389.0477

[H]⁺
m/z = 356.0376

[H - S]⁺
m/z = 315.0108
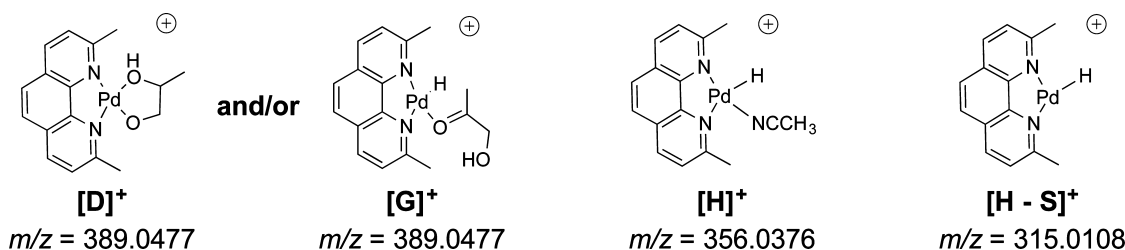
Figure 5. Ions observed by DESI-MS when a solution of **2** in CH₃CN was sprayed on a sample of **1**.
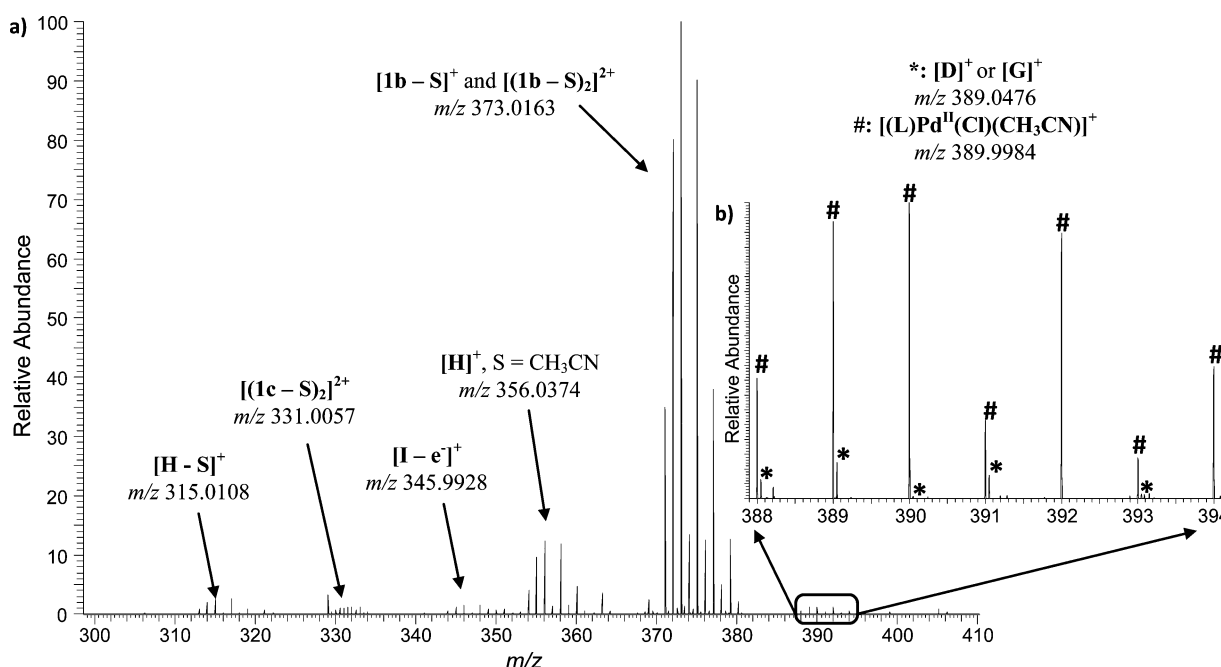
Figure 6. High-resolution DESI-MS spectrum of **1** (10 μL of 10 mM **1** deposited on paper) sprayed with a 0.1 M solution of **2** in CH₃CN: (a) Pd-containing species from *m/z* 295 to 415; (b) expansion of *m/z* 388−394 showing the resolved peaks for chelate **D** and/or ketone adduct **G**. L = neocuproine.

comparing both the isotope patterns and exact masses, all of which agreed within 5 ppm, with most of the peaks agreeing within 2 ppm (see Table S1 in the Supporting Information for assignments of Pd-containing species; the observed *m/z* values reported here are for the ¹⁰⁶Pd species). In the absence of

added 1,2-propanediol, the base peak corresponded to the cationic acetate complex [(L)Pd(OAc)]⁺ (L = neocuproine) ([**1b − S**]⁺, *m/z* 373.0163; Figure 4). Masses of other minor species corresponded to dimeric {[(L)Pd(OAc)]₂(OTf)}⁺ ([(**1b − S**)₂(**OTf**)]⁺, *m/z* 896.9864), {[(L)Pd(OH)]₂(OTf)}⁺

$([[(\mathbf{1c \cdot S})_2(\mathbf{OTf})]^+$, m/z 812.9648), $\{[(L)Pd(OH)(O)Pd(L)]^+$ $([\mathbf{J}]^+$, m/z 663.0046), and minor amounts of chloride-containing species that presumably arise from trace Cl^- in the solvent or from the fused silica capillary tubing used to transfer the spray solution (Figure 4).

Also observed in low abundance were ions at m/z 345.9930 and 314.0031, assigned as the dioxygen adduct $[(L)Pd^{III}(O_2)]^+$ $([\mathbf{I} - \mathbf{e}^-]^+$; Figures 2 and 4) and the Pd(I) species $[(L)Pd^I]^+$, respectively. Low-resolution CID studies of $[\mathbf{I} - \mathbf{e}^-]^+$ yielded $[(L)Pd^I]^+$ (m/z 314.1), corresponding to loss of O_2 (Figure S10 in the Supporting Information). These latter two ions were observed in the absence of a reducing agent (i.e., alcohol); their origin under these conditions is not clear at present.[89]

When a 0.1 M solution of 1,2-propanediol (**2**) in CH_3CN was sprayed onto a surface containing Pd complex **1**, ions corresponding to the cationic Pd hydrides $[(L)Pd(H)(S)]^+$ $([\mathbf{H}]^+$; S = CH_3CN, m/z 356.0376; S = none, m/z 315.0108; Figures 2, 5, and 6) were observed. Also observed, albeit in low abundance, were ions corresponding to $[(L)Pd(\mathbf{2})]^+$ $([\mathbf{D}]^+)$ and/or the isomeric $[(L)Pd(H)(hydroxyacetone)]^+$ $([\mathbf{G}]^+)$ (m/z 389.0477; Figures 2 and 5) and the dioxygen adduct $([\mathbf{I} - \mathbf{e}^-]^+$, m/z 345.9928; Figures 2 and 4) (Figure 6 and Table S2 in the Supporting Information). Significantly, neither of the Pd hydrides were observed in the absence of **2**, which provides indirect support for β-H elimination as a key step in the oxidation of 1,2-propanediol.

The DESI-MS results provide further support for the mechanism proposed in Figure 2, as several of the key intermediates proposed could be identified (See Figures 2, 4, and 5).[7,41] These studies illustrate the utility of DESI-MS as a method for identifying reactive intermediates that might be difficult to detect with other methods.

CONCLUSION

We have reported the highly chemoselective oxidation of polyols to α-hydroxy ketones using the cationic Pd neocuproine catalyst **1**. The mild conditions, high chemoselectivities, and high selectivity for mono-oxidation to the hydroxy ketones are attractive features of a strategy for the conversion of unprotected polyols to useful chemical intermediates. We have shown that the chemoselective alcohol oxidation catalyzed by **1** can be extended to include various unprotected polyols, including the tetraols erythritol and threitol. Preparative-scale oxidations with air/O_2 or benzoquinone as the terminal oxidant showed that polyols containing both primary and secondary alcohol moieties are oxidized exclusively at the secondary alcohol to form the corresponding hydroxy ketones. We also extended the substrate scope to include the lactonization of N-Boc-protected and ether-functionalized 1,5-diols, illustrating the versatility and tolerance of complex **1** for mediating chemoselective alcohol oxidation reactions.

Vicinal 1,2-diols are oxidized selectively at the secondary alcohol, despite the preference of this catalyst to oxidize primary alcohols in presence of secondary alcohols. The results of experimental and theoretical studies imply that the difference in chemoselectivity observed in the oxidation of 1,2-diols versus primary and secondary alcohols is due to differences in the rate-determining and product-determining steps. For vicinal diols, the facile formation of chelating protonated diolates (**D**) leads to both higher rates and high chemoselectivity for oxidation of the secondary alcohol to give the hydroxy ketone. Kinetic and theoretical studies suggest that product-determining β-H elimination from the secondary Pd alkoxide favors the hydroxy

ketone. In contrast, for mixtures of primary and secondary alkoxides, the selectivity observed for oxidation of primary alcohols to form aldehydes is most reasonably attributed to a product-determining equilibration between the cationic Pd acetates (**1b**/**1c**) and the Pd-alkoxides **A**, favoring the formation of the primary Pd alkoxide.

The present study highlights some key fundamental differences between mono-ol and polyol oxidation for alcohol oxidations involving β-H elimination from metal alkoxides as a key step. Application of these insights may facilitate the development of future selective oxidation reactions.

ASSOCIATED CONTENT

Ⓢ Supporting Information
Experimental and theoretical (DFT) methods, synthesis procedures, characterization data, DFT results, and animations depicting the DFT-computed imaginary-frequency modes of the transition-state structures **F** and **F'**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
waymouth@stanford.edu
Author Contributions
[†]K.C. and S.M.B. contributed equally.
Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) Parmeggiani, C.; Cardona, F. *Green Chem.* **2012**, *14*, 547.
(2) Muzart, J. *Tetrahedron* **2003**, *59*, 5789.
(3) Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006**, *62*, 8227.
(4) Arterburn, J. B. *Tetrahedron* **2001**, *57*, 9765.
(5) Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, *104*, 3037.
(6) Arends, I. W. C. E.; Sheldon, R. A. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, Germany, 2004.
(7) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774.
(8) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Brown Ripin, D. H. *Chem. Rev.* **2006**, *106*, 2943.
(9) Painter, R. M.; Pearson, D. M.; Waymouth, R. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9456.
(10) Maki, T.; Iikawa, S.; Mogami, G.; Harasawa, H.; Matsumura, Y.; Onomura, O. *Chem.—Eur. J.* **2009**, *15*, 5364.

(11) Bettucci, L.; Bianchini, C.; Filippi, J.; Lavacchi, A.; Oberhauser, O. *Eur. J. Inorg. Chem.* **2011**, 1797.

(12) Bettucci, L.; Bianchini, C.; Oberhauser, W.; Hsiao, T. H.; Lee, H. M. *J. Mol. Catal. A: Chem.* **2010**, 322, 63.

(13) Plietker, B.; Niggemann, M. *Org. Biomol. Chem.* **2004**, 2, 2403.

(14) Onomura, O.; Arimoto, H.; Matsumura, Y.; Demizu, Y. *Tetrahedron Lett.* **2007**, 48, 8668.

(15) Hoyos, P.; Sinisterra, J. V.; Molinari, F.; Alcantara, A. R.; De Maria, P. D. *Acc. Chem. Res.* **2010**, 43, 288.

(16) Bogevig, A.; Sunden, H.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, 43, 1109.

(17) Hanessian, S.; Roy, R. *J. Am. Chem. Soc.* **1979**, 101, 5839.

(18) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, 123, 3367.

(19) Plietker, B. *J. Org. Chem.* **2004**, 69, 8287.

(20) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, 43, 1112.

(21) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, 92, 919.

(22) Perlin, A. S. *Adv. Carbohydr. Chem. Biochem.* **2006**, 60, 183.

(23) Daccolti, L.; Detomaso, A.; Fusco, C.; Rosa, A.; Curci, R. *J. Org. Chem.* **1993**, 58, 3600.

(24) Plietker, B. *J. Org. Chem.* **2003**, 68, 7123.

(25) Plietker, B. *Org. Lett.* **2004**, 6, 289.

(26) Kwon, Y.; Birdja, Y.; Spanos, I.; Rodriguez, P.; Koper, M. T. M. *ACS Catal.* **2012**, 2, 759.

(27) Arends, I. W. C. E.; ten Brink, G.-J.; Sheldon, R. A. *J. Mol. Catal. A: Chem.* **2006**, 251, 246.

(28) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Adv. Synth. Catal.* **2002**, 344, 355.

(29) Steinhoff, B. A.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, 126, 11268.

(30) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, 43, 3400.

(31) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854.

(32) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, 39, 221.

(33) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, 70, 3343.

(34) Ebner, D. C.; Bagdanoff, J. T.; Ferreira, E. M.; McFadden, R. M.; Caspi, D. D.; Trend, R. M.; Stoltz, B. M. *Chem.—Eur. J.* **2009**, 15, 12978.

(35) Trend, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, 130, 15957.

(36) Melero, C.; Shishilov, O. N.; Alvarez, E.; Palma, P.; Campora, J. *Dalton Trans.* **2012**, 41, 14087.

(37) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **1998**, 39, 6011.

(38) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, 64, 6750.

(39) Barats, D.; Neumann, R. *Adv. Synth. Catal.* **2010**, 352, 293.

(40) Noronha, G.; Henry, P. M. *J. Mol. Catal. A: Chem.* **1997**, 120, 75.

(41) Conley, N. R.; Labios, L. A.; Pearson, D. M.; McCrory, C. C. L.; Waymouth, R. M. *Organometallics* **2007**, 26, 5547.

(42) Pearson, D. M.; Waymouth, R. M. *Organometallics* **2009**, 28, 3896.

(43) Pearson, D. M.; Conley, N. R.; Waymouth, R. M. *Organometallics* **2011**, 30, 1445.

(44) A small amount of side products generated in the oxidation of erythritol (**6**) could not be readily identified by ^{1}H NMR analysis.

(45) Niu, W.; Molefe, M. N.; Frost, J. W. *J. Am. Chem. Soc.* **2003**, 125, 12998.

(46) Tsuda, Y.; Hanajima, M.; Matsuhira, N.; Okuno, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1989**, 37, 2344.

(47) Kong, X.; Grindley, T. B. *Can. J. Chem.* **1994**, 72, 2405.

(48) Moonmangmee, D.; Adachi, O.; Shinagawa, E.; Toyama, H.; Theeragool, G.; Lotong, N.; Matsushita, K. *Biosci., Biotechnol., Biochem.* **2002**, 66, 307.

(49) Endo, Y.; Bäckvall, J.-E. *Chem.—Eur. J.* **2011**, 17, 12596.

(50) Murahashi, S.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, 52, 4319.

(51) Zhao, J.; Hartwig, J. F. *Organometallics* **2005**, 24, 2441.

(52) Zhang, J.; Balaraman, E.; Leitus, G.; Milstein, D. *Organometallics* **2011**, 30, 5716.

(53) Forschner, T. C. U.S. Patent 5,310,945, May 10, 1994.

(54) Schultz, M. J.; Park, C. C.; Sigman, M. S. *Chem. Commun.* **2002**, 3034.

(55) Libiszowski, J.; Kowalski, A.; Szymanski, R.; Duda, A.; Raquez, J. M.; Degee, P.; Dubois, P. *Macromolecules* **2004**, 37, 52.

(56) Lemieux, R. U.; Lown, J. W. *Can. J. Chem.* **1964**, 42, 893.

(57) Similar effects have been observed with (neocuproine) Pd(OAc)$_2$ in the oxidation of propanols, but there the selectivity for 1-propanol was observed only in single-vessel competition experiments (see ref 28).

(58) Schultz, M. J.; Adler, R. S.; Zierkiewicz, W.; Privalov, T.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, 127, 8499.

(59) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, 126, 9724.

(60) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G. B.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revisions A.02 and B.01; Gaussian, Inc.: Wallingford, CT, 2009.

(61) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, 41, 157.

(62) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, 72, 650.

(63) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, 82, 270.

(64) Ehlers, A. W.; Bohme, M.; Dapprich, S.; Gobbi, A.; Hollwarth, A.; Jonas, V.; Kohler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett.* **1993**, 208, 111.

(65) Optimizations and IRC analysis were also carried out using the CPCM solvent model for acetonitrile for the reaction coordinate yielding hydroxyacetone; single-point solvent calculations on gas-phase-optimized transition states were carried out for both the hydroxyacetone and lactaldehyde reaction coordinates (see Figures S13 and S14 in the Supporting Information).

(66) Brookhart, M.; Green, M. L. H.; Parkin, G. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, 104, 6908.

(67) Nielsen, R. J.; Keith, J. M.; Stoltz, B. M.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2004**, 126, 7967.

(68) Paavola, S.; Zetterberg, K.; Privalov, T.; Csoeregh, I.; Moberg, C. *Adv. Synth. Catal.* **2004**, 346, 237.

(69) Privalov, T.; Linde, C.; Zetterberg, K.; Moberg, C. *Organometallics* **2005**, 24, 885.

(70) When we used the smaller LANL2MB basis set, this intermediate was not found.

(71) Theofanis, P. L.; Goddard, W. A., III. *Organometallics* **2011**, 30, 4941.

(72) Zhao, J.; Hesslink, H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, 123, 7220.

(73) McDermott, J. X.; White, J. F.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, 98, 6521.

(74) McDermott, J. X.; White, J. F.; Whitesides, G. M. *J. Am. Chem. Soc.* **1973**, 95, 4451.

(75) Macgregor, S. A.; Vadivelu, P. *Organometallics* **2007**, 26, 3651.

(76) Sieffert, N.; Buhl, M. *J. Am. Chem. Soc.* **2010**, 132, 8056.

(77) Ifa, D. R.; Wu, C. P.; Ouyang, Z.; Cooks, R. G. *Analyst* **2010**, 135, 669.

(78) Cooks, R. G.; Ouyang, Z.; Takats, Z.; Wiseman, J. M. *Science* **2006**, 311, 1566.

(79) Roglans, A.; Pla-Quintana, A. In *Reactive Intermediates: MS Investigations in Solution*; Santos, L. S., Ed.; Wiley-VCH: Weinheim, Germany, 2010; p 229.

(80) Takats, Z.; Wiseman, J. M.; Gologan, B.; Cooks, R. G. *Science* **2004**, *306*, 471.

(81) Takats, Z.; Wiseman, J. M.; Cooks, R. G. *J. Mass Spectrom.* **2005**, *40*, 1261.

(82) Perry, R. H.; Splendore, M.; Chien, A.; Davis, N. K.; Zare, R. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 250.

(83) Perry, R. H.; Brownell, K. R.; Chingin, K.; Cahill, T. J.; Waymouth, R. M.; Zare, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 2246.

(84) Xu, G. M.; Chen, B.; Guo, B.; He, D. X.; Yao, S. Z. *Analyst* **2011**, *136*, 2385.

(85) Miao, Z. X.; Chen, H.; Liu, P. Y.; Liu, Y. *Anal. Chem.* **2011**, *83*, 3994.

(86) Perry, R. H.; Cahill, T. J.; Roizen, J. L.; Du Bois, J.; Zare, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 18295.

(87) Perry, R. H.; Cooks, R. G.; Noll, R. J. *Mass Spectrom. Rev.* **2008**, *27*, 661.

(88) Hu, Q. Z.; Noll, R. J.; Li, H. Y.; Makarov, A.; Hardman, M.; Cooks, R. G. *J. Mass Spectrom.* **2005**, *40*, 430.

(89) Detection of Pd^0 species as oxidized Pd^I is not uncommon in ESI-MS studies of Pd catalysis (see ref 79). Oxidation of suitable functional groups in paper was considered as a potential origin for **I** in experiments without substrate. However, studies performed by evaporating a solution of **1** directly on a glass slide still contained this peak. Also, the hydride **H** was not detected without addition of alcohol substrate, providing another indication that **1** did not detectably oxidize the paper surface under these conditions.