VOLUME 70, NUMBER 9

JOC Articles

APRIL 29, 2005

Development and Comparison of the Substrate Scope of Pd-Catalysts for the Aerobic Oxidation of Alcohols

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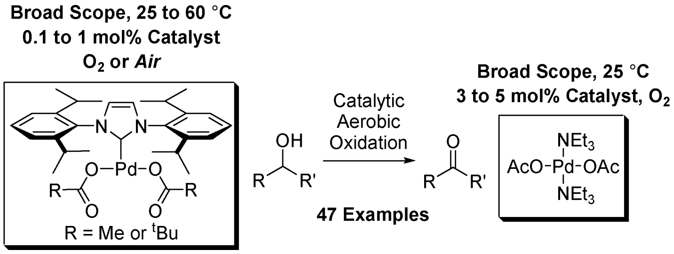
Received October 8, 2004



Three catalysts for aerobic oxidation of alcohols are discussed and the effectiveness of each is evaluated for allylic, benzylic, aliphatic, and functionalized alcohols. Additionally, chiral nonracemic substrates as well as chemoselective and diastereoselective oxidations are investigated. In this study, the most convenient system for the Pd-catalyzed aerobic oxidation of alcohols is $Pd(OAc)_2$ in combination with triethylamine. This system functions effectively for the majority of alcohols tested and uses mild conditions (3 to 5 mol % of catalyst, room temperature). $Pd(IiPr)(OAc)_2(H_2O)$ (**1**) also successfully oxidizes the majority of alcohols evaluated. This system has the advantage of significantly lowering catalyst loadings but requires higher temperatures (0.1 to 1 mol % of catalyst, 60 °C). A new catalyst is also disclosed, $Pd(IiPr)(OPiv)_2$ (**2**). This catalyst operates under very mild conditions (1 mol %, room temperature, and air as the O_2 source) but with a more limited substrate scope.

Introduction

The oxidation of alcohols to carbonyl compounds is an essential functional group transformation in organic synthesis. Countless methods have been developed to perform this reaction, with the most popular represented by the Collins,[1] Dess−Martin,[2] Jones,[3] Moffatt,[4] Parikh−Doering,[5] pyridinium chlorochromate (PCC),[6] pyridinium dichromate (PDC),[7] and Swern[8] oxidations. These oxidations have served the organic synthesis community well as highly versatile and robust methods. Unfortunately, most of these suffer from the use of stoichiometric toxic reagents, cryogenic conditions, and/or the production of copious amounts of waste. An alternative, more practical approach is the use of a catalyst in combination with a stoichiometric terminal oxidant. An excellent example of this is the use of catalytic tetrapropylammonium perruthenate (TPAP) with stoichiometric *N*-methylmorpholine (NMO) for the oxidation of alcohols.[9] While this

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[1] Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363−3363.
[2] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
[3] Harding, K. E.; May, L. M.; Dick, K. F. *J. Org. Chem.* **1975**, *40*, 1664−1665.
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10.1021/jo0482211 CCC: $30.25 © 2005 American Chemical Society
Published on Web 12/30/2004

system has proven very useful for the oxidation of a wide variety of alcohols, the use of stoichiometric NMO is not ideal.[10]

An attractive alternative terminal oxidant is molecular oxygen because it is readily available, inexpensive, and produces benign stoichiometric byproducts (H_2O_2 and/or H_2O). Due to these attributes, the development of catalysts for the aerobic oxidation of alcohols has been explored by using a diverse scope of metals which include Mn,[11] Fe,[12] Ru,[13] Co,[14] Cu,[15] Pt,[16] Zn,[17] Rh,[18] V,[19] Ce,[20] Ni,[21] Pd,[22,23] and bimetallic systems.[24] While many of these systems are synthetically useful, several drawbacks remain including the use of high catalyst loadings, forcing conditions, and/or lack of substrate scope. With the hope of addressing these issues, we have investigated the development of new Pd(II)-catalysts for the aerobic oxidation of alcohols.[25]

Significant effort has been afforded to the development of Pd-catalysts for the aerobic alcohol oxidations.[26-28] Of these reports, Uemura's pyridine/Pd(OAc)$_2$ system[29] and Sheldon's phananthroline/Pd(OAc)$_2$ system[30] under aqueous conditions serve as benchmarks in the development of new catalysts: Uemura's primarily due to the simplicity of the procedure and Sheldon's due to the effective use of low loadings of the homogeneous catalyst.[31] However, improved catalyst systems are desirable where a combination of lower catalyst loadings, lower levels of oxygen, and milder temperatures can be used. These improvements would potentially allow for applications in various areas including industrial oxidations and oxidations of complex targets.

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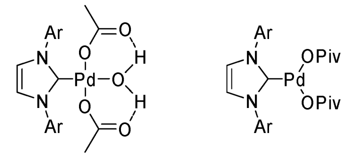
In this regard, we have recently reported two catalyst systems for the palladium-catalyzed aerobic oxidation of alcohols. In the first system, a mixture of Pd(OAc)$_2$ and triethylamine (TEA) was used to successfully oxidize a broad scope of alcohols *at room temperature*.[32] After disclosing this initial study, we used data from mechanistic studies performed by several groups including our own on aerobic alcohol oxidations to design and develop a highly active catalyst using an N-heterocyclic carbene (NHC) as the ligand for Pd, and acetate as both the anionic ligand and the internal base for successful oxidation.[33,34]

While these two catalyst systems provided significant advances in both practicality (room temperature and air atmosphere) and activity (up to 1000 turnovers) for the Pd-catalyzed aerobic oxidation of alcohols, developing a catalyst system that can combine the use of low temperatures, low catalyst loadings, and an air atmosphere is desirable. Also, the application of Pd-catalysis to the oxidation of more complex substrates bearing alcohols has been lacking. Herein, we report on the development of a new Pd(II) aerobic alcohol oxidation catalyst system and comparison of all three catalytic systems for general substrate scope, and scope relevant to the synthesis of complex targets.

Results and Discussion

Recently, we have disclosed a mechanistic study on the aerobic oxidation of alcohols using Pd(IiPr)(OAc)$_2$(H$_2$O) (**1**).[33i] In this study, it was found that using more basic carboxylates as the anionic ligand for Pd resulted in increased rates of oxidation. Applying this finding has led to the development of a third system for the Pd-catalyzed aerobic oxidation of alcohols in which acetate has been substituted by pivalate (PivO). The resulting catalytic system uses 1.0 mol % of catalyst loading of Pd(IiPr)(OPiv)$_2$ (**2**) along with 0.5 mol % of PivOH under an *air atmosphere at room temperature* to oxidize a variety of alcohols.



1 **2**

Ar = 2,6-di^{i}Pr-Phenyl

Evaluation of Substrate Scope

Oxidation of Benzylic Alcohols with Pd(OAc)$_2$/TEA. Generally, benzylic alcohols oxidize well using this system (Table 1). Electronics do not seem to play a significant role on isolated yields with both electron-rich and electron-poor benzylic alcohols oxidizing well. A hindered secondary alcohol **3k** also oxidizes under these conditions, albeit with a lower yield and an extended reaction time (entry 22). Of note, *p*-(methylthio)benzyl alcohol **3f** oxidizes poorly with Pd-black formation observed (entries 12). A potential limitation is with alcohols that can chelate the Pd(II) catalyst, either as a starting material or product, resulting in observed inhibition of oxidation (entries 28 and 30).

Oxidation of Benzylic Alcohols with 1. Benzylic alcohols are excellent substrates for this catalyst, with electron-rich alcohols having the fastest rates (Table 1).[34] Compared with the Pd(OAc)$_2$/TEA system, the sterically hindered alcohol **3k** oxidizes much more efficiently (entry 23). Also, *p*-(methylthio)benzyl alcohol **3f** oxidizes well under standard conditions, and with a slightly modified procedure provides a 90% isolated yield of the desired product with no oxidation of the sulfur (entries 13 and 14). Of practical significance, **1** can be prepared in situ from commercially available starting materials by using Pd(OAc)$_2$, IiPr-HBF$_4$, and KO^{t}Bu, to provide an effective oxidation (entry 2). For the oxidation of the electronically activated substrate, *p*-methoxybenzyl alcohol **3c**, the catalyst loading can be lowered to 0.1 mol % to provide complete conversion representing 1000 turnovers (entry 8). Once again, this oxidation system is not successful for the oxidation of **3m** and **3n** (entries 29 and 31).

By increasing the concentration of AcOH to 4 mol % on a 1-mmol scale, this oxidation system can be rendered effective for the oxidation of benzylic alcohols under *an air atmosphere* (entries 3, 7, 21, and 26). This was only the second example of a homogeneous Pd-catalyst effective for the oxidation of alcohols under ambient pressure of air.[27d] By using these modified conditions and increasing the AcOH additive from 4 mol % to 5 mol %, the oxidation of secphenethyl alcohol **3a** can be accomplished on a 1-g scale in 97% isolated yield (entry 3). The ability to modulate the catalysis by addition of AcOH allows the use of lower oxygen pressures and potential tuning of this system for a particular substrate.

Oxidation of Benzylic Alcohols with 2. This system compares well with both Pd(OAc)$_2$/TEA and **1** for the oxidation of benzylic alcohols. Once again primary, secondary, and cyclic benzylic alcohols oxidize to completion under very mild conditions (ambient temperature and air filled balloon) while using low catalyst loadings (1 mol %). However, an electron-deficient benzylic alcohol

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(31) Uemura's system has also been applied to other oxidation reactions: (a) For a review, see: Nishimura, T.; Ohe, K.; Uemura, S. *Synlett* **2004**, 201–216. (b) For ring opening of hydroxycyclopropanes, see: Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147–149. (c) For intramolecular oxidative amination, see: Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem.*, *Int. Ed.* **2002**, *41*, 164–166. (d) For Wacker cyclizations, see: Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem.*, *Int. Ed.* **2003**, *42*, 2892–2895. (e) For annulation of indoles, see: Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578–9579.

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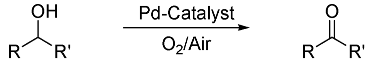
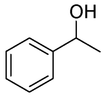
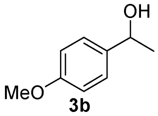
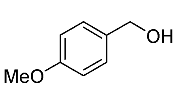
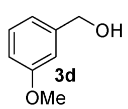
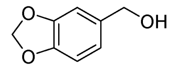
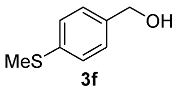
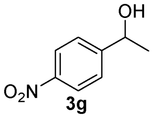
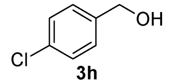
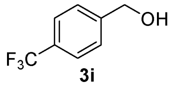
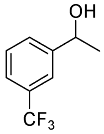
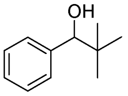
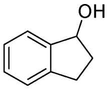
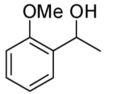
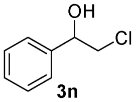
(35) This was previously illustrated by showing that the addition of cinnamaldehyde inhibited the oxidation of 2-decanol. See ref 32 for details.

TABLE 1. Oxidation of Benzylic Alcohols[a]



3a-n 4a-n

Entry	Alcohol	Catalyst[b-d]	Conversion (%)[e,f]
1	 3a	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	(93)
2[g]		0.5 mol% **1**, O_2, 60 °C, 5h 2 mol% AcOH	>99
3[h]		0.5 mol% **1**, Air, 60 °C, 14h 5 mol% AcOH	>99 (97)
4		1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	>99
6	 3b	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	(96)
7		0.5 mol% **1**, Air, 60 °C, 14h 4 mol% AcOH	>99 (93)
8	 3c	**0.1** mol% **1**, O_2, 60 °C, 20h 2 mol% AcOH	>99
9		1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	>99
10	 3d	1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	>99 (85)
11	 3e	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	(97)
12	 3f	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	35
13		0.5 mol% **1**, O_2, 60 °C, 13h 2 mol% AcOH	90
14		0.75 mol% **1**, O_2, 60 °C, 14h 5 mol% Bu_4NOAc	>95 (90)
15		1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	92
16	 3g	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	(85)
17	 3h	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	(93)
18	 3i	1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	47
19	 3j	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	(95)
20		0.5 mol% **1**, O_2, 60 °C, 12h 2 mol% AcOH	>99 (99)
21		0.5 mol% **1**, Air, 60 °C, 20h 4 mol% AcOH	>99
22	 3k	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	(50)
23		0.75 mol% **1**, O_2, 60 °C, 14h 5 mol% Bu_4NOAc	91
24		1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	23
25	 3l	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	(95)
26		0.5 mol% **1**, Air, 60 °C,14h 4 mol% AcOH	>99
27		1 mol% **2**, Air, rt, 12h 0.5 mol% PivOH	>99
28	 3m	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	<5
29		0.5 mol% **1**, O_2, 60 °C, 14h 2 mol% AcOH	<5
30	 3n	3 mol% $Pd(OAc)_2$ 6 mol% TEA, O_2, rt, 12h	<5
31		0.5 mol% **1**, O_2, 60 °C, 14h 2 mol% AcOH	<5

[a] See Experimental Section for details. [b] Reactions with $Pd(OAc)_2$/TEA: 0.3 M in 15% THF/toluene. [c] Reactions with **1**: 0.5 M in toluene. [d] Reactions with **2**: 0.4 M in toluene. [e] Conversion measured by GC or ^{1}H NMR. [f] Isolated yield in parentheses. [g] Catalyst **1** prepared in situ with 0.5 mol % of $Pd(OAc)_2$, 0.65 mol % of I*i*Pr-HBF_4, and 0.7 mol % of KO^{t}Bu. [h] 1.0-g scale.

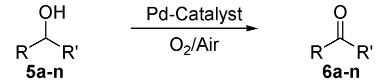
3i does not oxidize well (entry 18). This system also works well for the oxidation of *p*-(methylthio)benzyl alcohol **3f**, providing 92% conversion of the alcohol with no Pd-black formation (entry 15). The sterically encumbered benzylic alcohol **3k** only oxidizes to 23% conversion under the standard conditions showing a potential limitation of this system (entry 24).

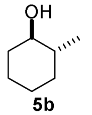
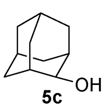
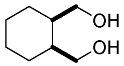
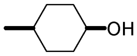
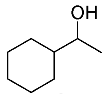
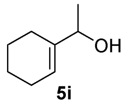
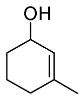
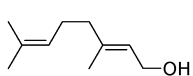
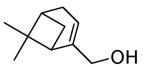
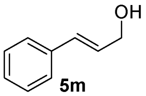
Oxidation of Aliphatic and Allylic Alcohols with $Pd(OAc)_2$/TEA. The oxidation of straight chain and cyclic secondary aliphatic alcohols under standard conditions is successful (Table 2). This includes oxidation of the sterically encumbered alcohol, 2-adamantanol **5c**, in a slightly lower yield. A 1,4-diol **5d** oxidizes to the corresponding lactone (entry 6). The oxidation also works well for primary aliphatic alcohols; however, the oxidation of straight chain, primary aliphatic alcohols requires modification of the standard conditions by lowering the substrate concentration (vide infra).

As with most Pd-catalyzed alcohol oxidations, allylic alcohols proved to be a more challenging substrate class. Cyclic allylic alcohol **5j** oxidizes well with this system but myrtenol **5l** only oxidizes to 82% conversion (entries 16 and 22). Straight chain, primary allylic alcohols do not oxidize well with this system even under various modified conditions (entries 19, 25, and 26). The difficulty with oxidation of allylic alcohols is attributed to the ability of α,β-unsaturated carbonyl compounds to chelate Pd(0), thus inhibiting oxidation.[35]

Oxidation of Aliphatic and Allylic Alcohols with 1. By decreasing the AcOH concentration from 2 mol % to 1 mol %, straight chain and cyclic aliphatic secondary alcohols oxidize well with 0.5 mol % **1** (Table 2). As with

TABLE 2. Oxidation of Aliphatic and Allylic Alcohols[a]



Entry	Alcohol	Catalyst^{b-e}	Conversion (%)^{f,g}
1	2-decanol **5a**	3 mol% Pd(OAc)$_2$ 6 mol% TEA, O$_2$, rt, 12h	(97)
2		0.5 mol% **1**, O$_2$, 60 °C, 13h 1 mol% AcOH	99 (93)
3		1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	97
4	 **5b**	3 mol% Pd(OAc)$_2$ 6 mol% TEA, rt, O$_2$, 12h	(98)
5	 **5c**	3 mol% Pd(OAc)$_2$ 6 mol% TEA, O$_2$, rt, 12h	(81)
6[h]	 **5d**	3 mol% Pd(OAc)$_2$ 6 mol% TEA, O$_2$, rt, 12h	(90)
7	 **5e**	0.5 mol% **1**, O$_2$, 60 °C, 13h 1 mol% AcOH	>99
8		0.5 mol% **1**, Air, 60 °C, 14h 2 mol% AcOH	96
9		1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	63
10	 **5f**	1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	>99 (89)
11[i]	1-dodecanol **5g**	3 mol% Pd(OAc)$_2$ 18 mol% TEA, O$_2$, rt, 12h	(85)
12		0.5 mol% **1**, O$_2$, 60 °C, 10h 5 mol% Bu$_4$NOAc	85 (76)
13	1-octadecanol **5h**	0.5 mol% **1**, O$_2$, 60 °C, 10h 5 mol% Bu$_4$NOAc	(85)
14	 **5i**	0.5 mol% **1**, O$_2$, 60 °C, 12h 2 mol% AcOH	91 (84)
15		1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	62
16	 **5j**	3 mol% Pd(OAc)$_2$ 6 mol% TEA, O$_2$, rt, 12h	(93)
17		0.5 mol% **1**, O$_2$, 60 °C, 12h 2 mol% AcOH	92
18		1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	>99
19	 **5k**	3 mol% Pd(OAc)$_2$ 6 mol% TEA, O$_2$, rt, 12h	33
20[j]		0.5 mol% **1**, O$_2$, 60 °C, 18h 5 mol% Bu$_4$NOAc	(72)
21		1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	68
22[i]	 **5l**	3 mol% Pd(OAc)$_2$ 18 mol% TEA, O$_2$, rt, 12h	82
23		0.5 mol% **1**, O$_2$, 60 °C, 20h 5 mol% Bu$_4$NOAc	97
24		1 mol% **2**, Air, rt, 14h 0.5 mol% PivOH	99
25	 **5m**	5 mol% Pd(OAc)$_2$ 50 mol% TEA, O$_2$, rt, 12h	(30)
26		5 mol% Pd(OAc)$_2$ 300 mol% TEA, O$_2$, rt, 12h	(39)

[a] See Experimental Section for details. [b] Reactions with Pd(OAc)$_2$/TEA: 0.3 M in 15% THF/toluene. [c] Reactions with **1** and secondary alcohols: 0.5 M in toluene. [d] Reactions with **1** and primary alcohols: 0.125 M in toluene. [e] Reactions with **2**: 0.4 M in toluene. [f] Conversion measured by GC or ^{1}H NMR. [g] Isolated yield in parentheses. [h] Product is the corresponding lactone. [i] 0.075 M in 20% THF/toluene with 1.0 mol % of Bu$_4$NOAc added. [j] 5.4:1 mixture of isomers measured by ^{1}H NMR.

benzylic alcohols, oxidation of secondary aliphatic alcohols could be performed under an air atmosphere (1 atm) with an increase in AcOH concentration, from 1 to 2 mol % (entry 8). Primary aliphatic alcohols proved more challenging. Further optimization led to lowering the molarity of the reaction and switching from AcOH to 5 mol % of Bu$_4$NOAc to obtain decanal and octadecanal in moderate yields (entries 12 and 13). In the case of benzylic and secondary aliphatic alcohols, it was found that adding small amounts of AcOH allowed for more consistent oxidation presumably by slowing the oxidation rate thus preventing catalyst decomposition. However, the use of additive AcOH in the oxidation of primary aliphatic alcohols resulted in slow oxidation possibly due to the formation of small amounts of overoxidized product, which would result in decreased oxidation rates. Added acid has been shown to slow the rate of oxidation through an inhibitory pathway.[33i] Additionally, while elucidating the mechanistic details, we observed a first-order rate dependence on [Bu$_4$OAc] but considerable decomposition of catalyst occurs at high levels of this additive. Therefore, in the case of primary aliphatic alcohols, small amounts of Bu$_4$NOAc were used to accelerate the oxidation thus resulting in improved yields of aldehyde. Allylic alcohols oxidize better with **1** than with Pd(OAc)$_2$/TEA. The secondary allylic alcohol **5i** and cyclic allylic alcohol **5j** both oxidize well under standard conditions (entries 14 and 17). Myrtenol **5l** and geraniol **5k** require modified conditions for successful oxidations (entries 20 and 23). Unfortunately, the oxidation product of geraniol shows a 5.4:1 mixture of cis/trans isomers.

Oxidation of Aliphatic and Allylic Alcohols with 2. Catalyst **2** oxidizes secondary aliphatic alcohols successfully, although the cyclic aliphatic alcohol **5e** did not oxidize to complete conversion (Table 2). Unfortunately, it was concluded that this catalyst was not suitable for the oxidation of primary aliphatic alcohols due to very slow conversion. We hypothesize that due to the steric bulk associated with the ligands of this catalyst, one of the pivalates may dissociate from **2**. This would render **2** the most Lewis acidic of the three catalysts explored and thereby more susceptible to product inhibition by good Lewis bases such as aldehydes. Although this catalyst system was unsuccessful for the oxidation of primary aliphatic alcohols, it performed better with allylic alcohols. Both myrtenol **5l** and a cyclic allylic alcohol **5j** oxidize to completion under standard conditions (entries 18 and 24). The secondary allylic alcohol **5i** only oxidizes to 62% conversion (entry 15). Geraniol **5k** oxidizes to 68% conversion but in contrast to oxidation with **1**, no double bond isomerization is observed under the milder conditions used for this catalyst system (entry 7).

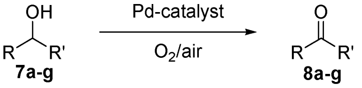
Functionalized Alcohols. As observed above, alcohols that have the ability to chelate with metals can be problematic substrates for oxidation. Inhibition of oxidation or decomposition of the catalyst is generally associated with these substrates. Unfortunately, this limits the use of several important substrate classes in Pd-catalyzed aerobic oxidations. Therefore, we were not enthusiastic about evaluating substrates that were more functionalized and related to the synthesis of complex targets. However, evaluation of monoprotected 1,2- and 1,3-diols proved fruitful, and many of these potentially chelating substrates worked well with all three catalysts as described below.

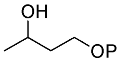
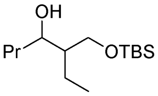
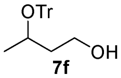
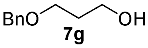
Oxidation of 1,3-Monoprotected Diols. For secondary alcohol substrates containing a protected primary alcohol, Pd(OAc)$_2$/TEA is the most versatile, giving excellent isolated yields of TBS **8a**, acetyl **8b**, trityl **8c**, and benzyl **8d** protected β-alkoxy-ketones (Table 3, entries 1, 4, 7, and 10). Of particular note, oxidation of **7d** proceeds well even on a 30-mmol (5.4 g) scale (entry 10) with no special considerations for the heterogeneous (gas/liquid) conditions employed. This system also effectively oxidizes the sterically encumbered alcohol **7e** in a 90% isolated yield (entry 13).

Using **1** proved to be a good catalyst for the oxidation of secondary alcohols containing a protected primary alcohol, yielding slightly lower conversions than the TEA system for TBS, trityl, and benzyl protected diols (Table 3, entries 2, 5, 8, and 11). Catalyst **2** did not oxidize secondary alcohols containing a protected primary alcohol as efficiently as the other catalysts. TBS and benzyl protected diols oxidize to moderate conversions while the acetyl and trityl protected alcohols are poorer substrates (entries 3, 6, 9, and 12). For a primary alcohol containing a protected secondary alcohol **7f**, both Pd(OAc)$_2$/TEA and **1** oxidize the trityl protected alcohol in >90% conversion (entries 16 and 17). However, a primary alcohol with a benzyl protected secondary alcohol **7g** was not as successful, presumably due to chelation (entries 18 and 19). Catalyst **2** does not oxidize primary, nonbenzylic alcohols. It is important to note, changing the nature of the protecting group has little impact on the ability to oxidize the substrate especially when using Pd(OAc)$_2$/TEA.

Oxidation of 1,2-Monoprotected Diols. For secondary alcohols containing a TBS **9a** or trityl **9c** protected alcohol, good yields of the desired ketones are achieved by using the Pd(OAc)$_2$/TEA oxidation system (Table 4, entries 1 and 7). In contrast, secondary alcohol **9b**, with an acetyl protecting group, does surprisingly poorly with the Pd(OAc)$_2$/TEA but **1** promotes complete conversion and a 99% isolated yield (entry 4). Catalyst **2** did not oxidize these alcohols with comparable efficiency to Pd(OAc)$_2$/TEA or **1**. For oxidation of the enantiomerically enriched substrate **9d**, containing a primary alcohol and a trityl protected secondary alcohol, Pd(OAc)$_2$/TEA and **1** both perform equally well with an 85% yield of the aldehyde when using Pd(OAc)$_2$/TEA (entries 10 and 11). In addition, the product was obtained with no racemiza-

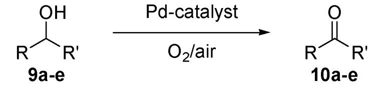
TABLE 3. Oxidation of 1,3 Monoprotected Diols

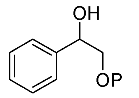
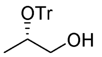
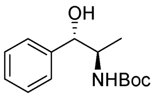


Entry	Substrate	Catalyst[a-d]	Time (h)	Yield (%)[e]
1	 P=TBS **7a**	4 mol% Pd(OAc)$_2$ 8 mol% TEA, O$_2$, rt	12	>99 (95)
2		1 mol% **1**, O$_2$, 60 °C 1 mol% AcOH	14	93
3		1 mol% **2**, Air, rt 0.5 mol% PivOH	13	80
4	P=Ac **7b**	5 mol% Pd(OAc)$_2$ 10 mol% TEA, O$_2$, rt	18	>99 (92)
5		1 mol% **1**, O$_2$, 60 °C 1 mol% AcOH	14	78
6		1 mol% **2**, Air, rt 0.5 mol% PivOH	15	51
7	P=Tr **7c**	5 mol% Pd(OAc)$_2$ 10 mol% TEA, O$_2$, rt	12	(92)
8		0.5 mol% **1**, O$_2$, 60 °C 1 mol% AcOH	13	94
9		1 mol% **2**, Air, rt 0.5 mol% PivOH	15	76
10[g]	P=Bn **7d**	4 mol% Pd(OAc)$_2$ 8 mol% TEA, O$_2$, rt	14	>99 (97)
11		0.5 mol% **1**, O$_2$, 60 °C 1 mol% AcOH	14	92
12		1 mol% **2**, Air, rt 0.5 mol% PivOH	15	91
13	 **7e**	5 mol% Pd(OAc)$_2$ 10 mol% TEA, O$_2$, rt	16	(90)
14		0.5 mol% **1**, O$_2$, 60 °C 1 mol% AcOH	14	>95
15		1 mol% **2**, Air, rt 0.5 mol% PivOH	18	66
16[h]	 **7f**	5 mol% Pd(OAc)$_2$ 10 mol% TEA 1 mol% Bu$_4$NOAc, O$_2$, rt	12	(91)
17		1 mol% **1**, O$_2$, 60 °C 5 mol% Bu$_4$NOAc	13	94
18[h]	 **7g**	4 mol% Pd(OAc)$_2$ 24 mol% TEA 1 mol% Bu$_4$NOAc, O$_2$, rt	15	69
19		0.5 mol% **1**, O$_2$, 60 °C 5 mol% Bu$_4$NOAc	15	46

[a] Reactions with Pd(OAc)$_2$/TEA: 0.3 M in 15% THF/toluene. [b] Reactions with **1** and secondary alcohols: 0.5 M in toluene. [c] Reactions with **1** and primary alcohols: 0.125 M in toluene. [d] Reactions with **2**: 0.4 M in toluene. [e] Isolated yield in parentheses. [f] Conversion measured by GC or ^{1}H NMR. [g] 30-mmol scale. [h] 0.075 M in 20% THF/toluene.

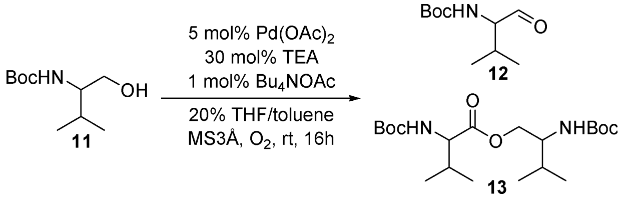
TABLE 4. Oxidation of 1,2 Monoprotected Diols and Amino Alcohols



Entry	Substrate	Catalyst[a-c]	Time (h)	Yield (%)[d,e]
1	 P=TBS **9a**	5 mol% $Pd(OAc)_2$ 10 mol% TEA, O_2, rt	15	>99 (88)
2		1 mol% **1**, O_2, 60 °C 2 mol% AcOH	14	78
3		1 mol% **2**, Air, rt 0.5 mol% PivOH	19	80
4	P=Ac **9b**	4 mol% $Pd(OAc)_2$ 8 mol% TEA, O_2, rt	13	69
5		1 mol% **1**, O_2, 60 °C 2 mol% AcOH	14	>99 (99)
6		1 mol% **2**, Air, rt 0.5 mol% PivOH	14	56
7	P=Tr **9c**	5 mol% $Pd(OAc)_2$ 10 mol% TEA, O_2, rt	18	(94)
8		1 mol% **1**, O_2, 60 °C 2 mol% AcOH	13	91
9		1 mol% **2**, Air, rt 0.5 mol% PivOH	14	68
10[f,g]	 **9d**	5 mol% $Pd(OAc)_2$ 15 mol% TEA, O_2, rt 1 mol% Bu_4NOAc	18	(85)
11[f,h]		0.5 mol% **1**, O_2, 60 °C 5 mol% Bu_4NOAc	15	92
12[f]	 **9e**	5 mol% $Pd(OAc)_2$ 10 mol% TEA, O_2, rt	15	(97)
13[i]		1 mol% **1**, O_2, 60 °C 2 mol% AcOH	14	63
14[f]		1 mol% **2**, Air, rt 0.5 mol% PivOH	14	89

[a] Isolated yield in parentheses. [b] Reactions with $Pd(OAc)_2$/TEA: 0.3 M in 15% THF/toluene. [c] Reactions with **1**: 0.5 M in toluene. [d] Reactions with **2**: 0.4 M in toluene. [e] Conversion measured by GC or by ^1H NMR. [f] No racemization of the product is observed. [g] 0.1 M. [h] 0.125 M. [i] Racemized from 99% to 97% ee.

TABLE 5. Preventing Ester Formation of 1,2-Amino Alcohols



entry	modified conditions	% conversion	**12**:**13**[a]
1[b]	0.075 M	70	4.5:1
2	0.1 M	75	3.1:1
3	0.125 M	76	2.3:1
4	10% THF	77	3.6:1
5	50% THF	70	6.6:1
6	100% THF	70	21:1
7	15 mol % of TEA	75	3.6:1
8	60 mol % of TEA	69	7.0:1
9	100 mol % TEA	64	9.4:1
10	100% of THF/100 mol % of TEA	56	34:1
11[c,d]	$Pd(liPr)(OAc)_2(H_2O)$	36	33:1

[a] Ratio determined by GC and accounts for differences in response factors. [b] No racemization is observed. [c] 0.75 mol % of **1**. [d] Complete racemization observed.

tion. Overall, 1,2-monoprotected diols are viable substrates for Pd-catalyzed aerobic oxidative protocols.

Protected 1,2-Amino Alcohols. While unprotected amino alcohols will not oxidize with these catalyst systems, protecting the amine may allow for facile alcohol oxidation. To test this, norephedrine was Boc protected and submitted to the oxidation conditions (Table 4, entries 12–14). As with most functionalized alcohols, $Pd(OAc)_2$/TEA outperformed the other catalysts providing a 97% yield of the desired α-amino-ketone. No racemization of **10e** is observed with the two methods at room temperature but a slight erosion of enantiomeric excess (99% to 97% ee) is observed with catalyst **1** at 60 °C. A more difficult substrate, *N*-boc-valinol **11**, was tested with the $Pd(OAc)_2$/TEA catalyst system where the aldehyde is obtained in modest conversion with no loss of stereochemical integrity. However, a major byproduct **13**, the ester formed from two molecules of *N*-boc-valinol, was observed (Table 5). This observation was not entirely surprising considering primary aliphatic alcohols required modified reaction conditions for effective oxidation. However, while ester formation was observed for other primary aliphatic alcohols, the relative ratios of aldehyde to ester were much less significant (>20:1). In the case of *N*-boc-valinol, substantially more ester is formed under these conditions (Table 5, entry 1). We reasoned the undesired enhancement of ester formation is attributed to the ability of the resulting aldehyde to chelate to the Pd catalyst. Lewis acid activation allows for nucleophilic attack of an alcohol on the aldehyde to result in a new Pd-alkoxide derived from the hemiacetal. Subsequent β-hydride elimination leads to ester formation. Presumably, this mechanism is responsible for lactone formation from a γ-diol via an intramolecular path (Table 2, entry 6). In the current study, ester formation is not a desirable product but the design of a system that converts alcohols directly to the acid oxidation state is currently under study.[36]

To test if chelation is the most likely contributor to the increased ester formation, we evaluated several modified reaction conditions. It was found that ester formation can be limited by increasing the concentration of competing ligands in the reaction by raising the THF and/or TEA concentration (Table 5, entries 4–10). Additionally, lowering the entropic barrier by decreasing the molarity of the substrate leads to modest improvements (Table 5, entries 1–3). While improvements in the ratio of aldehyde to ester are observed, a corresponding slowing of the oxidation rate also results, leading to a more selective but inefficient oxidation. The use of **1** for the oxidation of *N*-boc-valinol was also ineffective and leads to complete racemization of the aldehyde product. This *N*-boc protected α-amino primary alcohol is a difficult substrate for these Pd-catalyzed alcohol oxidations.

Chemoselective Alcohol Oxidations. Chemoselectivity in alcohol oxidations avoids the use of protecting groups and streamlines the chemical synthesis process. There are very few examples of highly chemoselective

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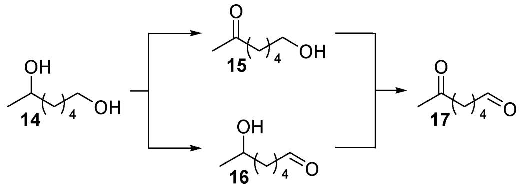
(36) Mueller, J. A.; Heaton, A. L.; Sigman M. S. Unpublished results.

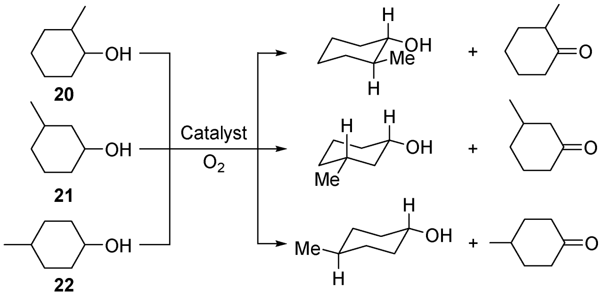
TABLE 6. Chemoselective Alcohol Oxidations



entry	conditions	% conversion	**15**:**16**:**17**^{a}
1	3 mol % of Pd(OAc)$_2$/6% TEA 0.3 M, 15% THF/toluene 3 Å MS, O$_2$, rt, 15 h	88	2.3:0.4:1
2	3 mol % of Pd(OAc)$_2$/18% TEA 0.075 M, 20% THF/toluene 3 Å MS, O$_2$, rt, 15 h	98	0.8:0.7:1
3	0.75 mol % of **1**, 5 mol % of Bu$_4$NOAc 0.7 M, toluene 3 Å MS, O$_2$, 60 °C, 15 h	75	2.6:2.4:1

[a] Ratio determined by GC and does not account for differences in response factors.

TABLE 7. Diastereoselective Oxidations of Methylcyclohexanols

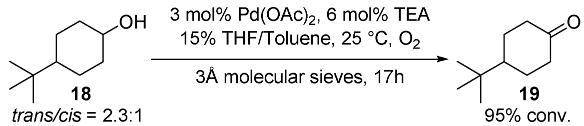


entry	catalyst	alcohol	time	conversion^a	trans:cis	s^b
1	Pd(OAc)$_2$/TEA		15	>99	NA	NA
2	**1**	**20**^{c}	13	48	65:1	11
3	**2**		16	45	575:1	23
4	Pd(OAc)$_2$/TEA		15	>99	NA	NA
5	**1**	**21**^{d}	13	51	1:22	7
6	**2**		16	40	1:25	19
7	Pd(OAc)$_2$/TEA		15	99	NA	NA
8	**1**	**22**^{e}	13	49	10:1	7
9	**2**		16	47	11:1	9

[a] GC conversion. [b] $s = \mathrm{Ln}(([\mathrm{minor}]/[\mathrm{minor}]_o)/([\mathrm{major}]/[\mathrm{major}]_o))$ where $[\mathrm{major}]_o$ and $[\mathrm{minor}]_o$ are initial concentrations of each isomer. [c] Starting material trans/cis ratio = 2.4:1, ratios measured by GC. [d] Starting material cis/trans ratio = 2.2:1, ratios measured by ^{1}H NMR. [e] Starting material trans/cis ratio = 1.6:1, ratios measured by ^{1}H NMR.

catalysts for alcohol oxidations.[37] Chemoselectivity, between a primary and a secondary alcohol, was tested by submitting 1,6-heptanediol **14** to oxidation with all three catalyst systems (Table 6). Conditions developed to oxidize secondary alcohols for the Pd(OAc)$_2$/TEA system lead to a chemoselective oxidation of the secondary alcohol to yield a nearly 6 to 1 ratio of **15** to **16** (entry 1). Significant oxidation to **17** is also observed making this a less practical method for chemoselective oxidation. In contrast, using conditions developed to oxidize primary alcohols yields almost equal amounts of **15**, **16**, and **17** (entry 2). In comparison, using conditions developed for oxidation of primary aliphatic alcohols with catalyst **1**, no chemoselectivity for the initial oxidation to **15** and **16** is observed but the oxidation to **17** is slower (entry 3). Testing of other conditions with catalysts **1** and **2** was severely limited by the solubility of the substrate in toluene.

Diastereoselective Oxidations of Substituted Cyclohexanols. When oxidizing 4-methylcyclohexanol with catalyst **1**, the cis isomer oxidized rapidly while the trans isomer oxidized considerably slower. An initial hypothesis was the alcohol must assume the axial position to undergo β-hydride elimination. A cis/trans mixture of 4-*tert*-butylcyclohexanol **18** was chosen as a model substrate to test this hypothesis. The cis diastereomer of the mixture, which is locked in the axial position, was expected to oxidize faster than the trans diastereomer. However, submitting the isomeric mixture of **18** to standard conditions for catalyst **1** gave no oxidation. In contrast, Pd(OAc)$_2$/TEA oxidizes **18** effectively but no diastereoselectivity is observed (eq 1).



(1)

Considering substrate **18** does not oxidize with catalyst **1**, we chose to explore the original hypothesis by oxidizing cis/trans mixtures of the three constitutional isomers of methyl cyclohexanol (Table 7). Using Pd(OAc)$_2$/TEA, complete oxidation of the mixture of diastereomers results and no diastereoselectivity is observed even at low conversions. In contrast, catalyst **1** promotes a highly diastereoselective oxidation of each alcohol. For 2- and 4-methylcyclohexanol, the cis isomer oxidizes faster whereas the trans isomer of 3-methylcyclohexanol oxidizes faster. The isomers corresponding to the fast reacting diastereomers contain a substituent in an axial position. Out of the three constitutional isomers, *cis*/*trans*-2-methylcyclohexanol results in the best resolutions. Using catalyst **1** a 65 to 1 ratio (selectivity factor = 11) of trans to cis diastereomers at 48% conversion is observed (entry 2). Catalyst **2** oxidizes all three alcohols in higher diastereoselectivity than catalyst **1** with **20** giving an excellent resolution of 575 to 1 ratio (selectivity factor = 23) of trans to cis diastereomers at 45% conversion (entry 3).

Interactions between the ligand, carboxylate, and substrate play a role in diastereoselectivity of the oxidation. As the substitution on the cyclohexane ring becomes closer to the site of oxidation, higher selectivity factors are observed. The size difference between the carboxylates on **1** and **2** leads to an enhancement of the selectivity factor as well. Even with these trends, it is difficult to propose a model when a change in rate-limiting step from β-hydride elimination to deprotonation for the different isomers is possible. Considering the implications to asymmetric catalysis, investigation of these possibilities will be a subject of future research.

Conclusions

The current systems compare favorably to the benchmarks established by Uemura and Sheldon. Chief among

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[37] For a recent review, see: Arterburn, J. B. *Tetrahedron* **2001**, *57*, 9765–9788.

the advantages are the mild conditions employed and higher catalytic activity for **1** and **2**. The mild nature of the reaction conditions presented herein allows oxidation of functionalized substrates with protecting groups which would likely not withstand the forcing conditions in other Pd-catalyzed aerobic alcohol oxidations.

Of the three catalysts, catalyst **2** uses the mildest reaction conditions (room temperature, 1 mol % of catalyst, and air as the O_2 source) but the substrate scope of this catalyst is the most limited. In comparison, catalyst **1** and $Pd(OAc)_2$/TEA both prove quite effective for a broad scope of substrates. The advantages of catalyst **1** are (1) low catalyst loadings for a Pd-catalyzed alcohol oxidation (0.1 to 1.0 mol %), (2) replacement of O_2 with ambient air by raising [AcOH] (2 to 5 mol %), (3) a diastereoselective oxidation of substituted cyclohexanols, and (4) effective oxidation of allylic alcohols. The advantages of the $Pd(OAc)_2$/TEA system are (1) simplicity of the reaction procedure, (2) the use of ambient temperature, (3) lack of racemization of nonracemic substrates, (4) moderately chemoselective oxidations, (5) easy scalability (30 mmol), and (6) generally excellent yields for functionalized alcohols. The main limitations of these systems are (1) the use of basic groups inhibit the oxidation and (2) substrate solubility in the reaction solvent. Even though catalysts **1** and **2** are more efficient in terms of catalyst loading and oxygen concentration, $Pd(OAc)_2$/TEA is the easiest system for evaluating a new substrate due to readily available reagents and good substrate scope. However, catalyst **1** has the greatest ability to be modulated through changing temperature, the oxygen concentration, and amounts of additive AcOH or Bu_4NOAc. Overall, these systems showed diverse scope and excellent reactivity under mild conditions.

The major challenge in developing efficient catalysts for Pd-catalyzed aerobic alcohol oxidations has been the identification of effective and stable ligands, especially considering that phosphine ligands are susceptible to oxidation under aerobic conditions. However, the current study showcases that the careful selection of ligand/base leads to excellent results in Pd-catalyzed aerobic oxidations. Using the knowledge that excess tertiary amine is necessary for effective oxidations and leads to inhibition of oxidation rates, we designed a catalyst that uses a single NHC ligand on $Pd(OAc)_2$. This allowed for significantly lower catalyst loadings. In addition, the catalytic activity of **1** was improved by changing the nature of the carboxylate anionic ligand from acetate to pivalate. Not only can the carboxylate be tuned, it is also possible to modify the NHC ligands electronically and structurally for development of desired reactivity. Considering this, future work in our laboratory is focused on the discovery of new Pd(II)-catalyzed oxidation reactions with applications in asymmetric catalysis with related ligands and catalyst design approaches.

Experimental Section

General Considerations. The alcohols used as substrates, HOAc, and Bu_4NOAc were purchased and used as received. $[Pd(IiPr)Cl_2]_2$[28f] and **1**[34] were prepared according to literature methods. $PhCH_3$ used as solvent was dried before use by passing through a column of activated alumina. THF was dried by distilling from sodium benzophenone ketyl. TEA is purified via distillation from CaH_2. The 3 Å molecular sieves were powdered and activated by placing them under vacuum in a flask and heating with a Bunsen burner for ca. 2 min. GC conversions for reactions with <99% conversion were determined relative to undecane or tetradecane as internal standard.

Preparation of $Pd(IiPr)(OPiv)_2$ (2). To a 20-mL scintillation vial was added 30 mg of $[Pd(IiPr)Cl_2]_2$ (0.027 mmol, 1.0 equiv) and 22.7 mg of AgOPiv (0.108 mmol, 4.025 equiv). In the dark (wrapped in aluminum foil), 6 mL of cooled CH_2Cl_2 (0 °C) was added and the mixture was allowed to slowly warm to room temperature. After 12 h, the reaction mixture was concentrated to ca. 2 mL and placed in a 2-mL microcentrifuge tube. The tube was placed in a centrifuge and spun for ca. 3 min. The yellow solution was transferred into a 10-mL flask and the solvent removed in vacuo to yield 35 mg of a yellow solid (96% yield). Mp >161 °C dec; IR (KBr) 2967, 2928, 2868, 1628, 1559, 1477, 1465, 1415, 1363, 1207 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 0.91 (s, 18 H), 1.1 (d, $J = 7.25$ Hz, 12H), 1.4 (d, $J = 6.87$ Hz, 12H), 2.70 (apparent sept., $J = 6.78$ Hz, 4H), 7.17 (s, 2H), 7.40−7.49 (m, 4H), 7.55−7.65 (m, 2H); ^{13}C NMR (CD_2Cl_2) δ 23.0, 25.7, 27.1, 28.5, 39.5, 124.3, 126.2, 130.5, 135.0, 146.3, 148.7, 192.5. Elemental Anal. Calcd: C 63.74, H 7.81, N 4.02. Found: C 63.76, H 7.72, N 3.91.

$Pd(OAc)_2$/TEA-Catalyzed Oxidation of Benzylic, Secondary Aliphatic, and Cylic Allylic Alcohols. To a 25-mL round-bottom flask equipped with a stir bar was added 6.7 mg of $Pd(OAc)_2$ (0.03 mmol, 0.03 equiv) and 200 mg of powdered, freshly activated 3 Å molecular sieves. To this was added 0.5 mL of THF, 2.83 mL of toluene, and 8.4 μL of TEA (0.06 mmol, 0.06 equiv). A balloon of oxygen was attached via a three-way joint. The flask was evacuated and refilled with oxygen three times followed by **vigorous** stirring for 30 min at room temperature under O_2. To this solution was added 1 mmol of alcohol and the mixture was stirred **vigorously** at room temperature under a balloon of O_2. The reaction progress was monitored by GC. After 12 h, the reaction mixture was placed directly on a plug of silica, washed with pentane to remove toluene, and eluted with diethyl ether. The ether was removed in vacuo to yield the desired carbonyl product. For alcohols with incomplete oxidation, the desired carbonyl product was isolated via column chromatography with mixtures of diethyl ether/hexanes as the eluting solvent. Purity was confirmed by NMR.

$Pd(OAc)_2$/TEA-Catalyzed Oxidation of Primary Aliphatic Alcohols. To a 50-mL round-bottom flask equipped with a stir bar was added 6.7 mg of $Pd(OAc)_2$ (0.03 mmol, 0.03 equiv) and 250 mg of powdered, freshly activated 3 Å molecular sieves. To this was added 2.6 mL of THF, 9.4 mL of toluene, 1.0 mL of 0.01 M Bu_4NOAc/toluene (0.01 mmol, 0.01 equiv), and 25 μL of TEA (0.18 mmol, 0.18 equiv). A balloon of oxygen was attached via a three-way joint. The flask was evacuated and refilled with oxygen three times followed by **vigorous** stirring for 30 min at room temperature under O_2. To this solution was added 1 mmol of alcohol and the mixture was stirred **vigorously** at room temperature under a balloon of O_2. The reaction progress was monitored by GC. After 12 h, the reaction mixture was placed directly on a plug of silica, washed with pentane to remove toluene, and eluted with diethyl ether. The ether was removed in vacuo to yield the desired carbonyl product. For alcohols with incomplete oxidation, the desired carbonyl product was isolated via column chromatography with diethyl ether/hexanes as the eluting solvent. Purity was confirmed by NMR.

$Pd(IiPr)(OAc)_2(H_2O)$-Catalyzed Oxidation of Benzylic and Secondary Allylic Alcohols. To a 10-mL round-bottom flask equipped with a stir bar was added 3.2 mg of $Pd(IiPr)(OAc)_2(H_2O)$ (0.005 mmol, 0.005 equiv) and 150 mg of powdered, freshly activated 3 Å molecular sieves. To this was added 1.6 mL of toluene and 0.4 mL of 0.1 M AcOH/toluene (0.02 mmol, 0.02 equiv) followed by 1 mmol of alcohol. A reflux condenser was attached to the flask and a balloon of oxygen was attached to the top of the condenser via a three-way joint.

The flask was evacuated and refilled with oxygen three times followed by **vigorous** stirring for ca. 10 min. The apparatus was placed in a 60 °C oil bath. The reaction progress was monitored by GC. After completion, the reaction mixture was cooled to ambient temperature and placed directly on a plug of silica, washed with pentane to remove toluene, and eluted with diethyl ether. The diethyl ether was removed in vacuo to yield the desired carbonyl product. For alcohols with incomplete oxidation, the desired carbonyl product was isolated via column chromatography with mixtures of diethyl ether/hexanes as the eluting solvent. Purity was confirmed by NMR.

Pd(IiPr)(OAc)$_2$(H$_2$O)-Catalyzed Oxidation of Secondary Aliphatic Alcohols. To a 10 mL round-bottom flask equipped with a stir bar was added 3.2 mg of **1** (0.005 mmol, 0.005 equiv) and 150 mg of powdered, freshly activated 3 Å molecular sieves. To this was added 1.8 mL of toluene and 0.2 mL of 0.1 M AcOH/toluene (0.01 mmol, 0.01 equiv) followed by 1 mmol of alcohol. A reflux condenser was attached to the flask and a balloon of oxygen was attached to the top of the condenser via a three-way joint. The flask was evacuated and refilled with oxygen three times followed by **vigorous** stirring for ca. 10 min. The apparatus was placed in a 60 °C oil bath. The reaction progress was monitored by GC. After completion, the reaction mixture was cooled to ambient temperature and placed directly on a plug of silica, washed with pentane to remove toluene, and eluted with diethyl ether. The diethyl ether was removed in vacuo to yield the desired carbonyl product. For alcohols with incomplete oxidation, the desired carbonyl product was isolated via column chromatography with mixtures of diethyl ether/hexanes as the eluting solvent. Purity was confirmed by NMR.

Pd(IiPr)(OAc)$_2$(H$_2$O)-Catalyzed Oxidation of Primary Aliphatic and Allylic Alcohols. To a 50-mL round-bottom flask equipped with a stir bar was added 4.7 mg of Pd(IiPr)(OAc)$_2$(H$_2$O) (0.0075 mmol, 0.0075 equiv), 15.1 mg of Bu$_4$NOAc (0.05 mmol, 0.05 equiv), and 200 mg of powdered, freshly activated 3 Å molecular sieves. To this was adde 10.0 mL of toluene followed by 1 mmol of alcohol. A reflux condenser was attached to the flask and a balloon of oxygen was attached to the top of the condenser via a three-way joint. The flask was evacuated and refilled with oxygen three times followed by **vigorous** stirring for ca. 10 min. The apparatus was placed in a 60 °C oil bath. The reaction progress was monitored by GC. After completion, the reaction mixture was cooled to ambient temperature and placed directly on a plug of silica, washed with pentane to remove toluene, and eluted with diethyl ether. The diethyl ether was removed in vacuo to yield the desired carbonyl product. For alcohols with incomplete oxidation, the desired carbonyl product was isolated via column chromatography with mixtures of diethyl ether/hexanes as the eluting solvent. Purity was confirmed by NMR.

Pd(IiPr)(OPiv)$_2$-Catalyzed Oxidation of Benzylic, Allylic, and Secondary Aliphatic Alcohols. To a 25-mL round-bottom flask equipped with a stir bar was added 7.2 mg of Pd(IiPr)(OPiv)$_2$ (0.01 mmol, 0.01 equiv) and 250 mg of powdered, freshly activated 3 Å molecular sieves. To this was added 2.45 mL of toluene and 0.05 mL of 0.1 M PivOH/toluene (0.005 mmol, 0.005 equiv). A balloon of air was attached via a three-way joint and the mixture was allowed to stir for 5 min. To the mixture was added 1 mmol of alcohol and the reaction mixture was stirred **vigorously**. The reaction progress was monitored by GC. After completion, the reaction mixture was cooled to ambient temperature and placed directly on a plug of silica, washed with pentane to remove toluene, and eluted with diethyl ether. The diethyl ether was removed in vacuo to yield the desired carbonyl product. For alcohols with incomplete oxidation, the desired carbonyl product was isolated via column chromatography with mixtures of diethyl ether/hexanes as the eluting solvent. Purity was confirmed by NMR.

Acknowledgment. This work was supported by the National Institutes of Health (NIGMS #RO1 GM63540), Pfizer GRD, and the Dreyfus Foundation (Teacher-Scholar Award). D.R.J. thanks the University of Utah and the ACS Organic Division Fellowship sponsored by the Schering Plough Research Institute for graduate research fellowships. S.S.H. thanks Pfizer GRD for a summer research fellowship. We thank Johnson Matthey for supplies of various palladium salts. We thank Professor Ilya Zharov for designing the cover artwork.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0482211