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Palladium-Catalyzed Olefin Dioxygenation

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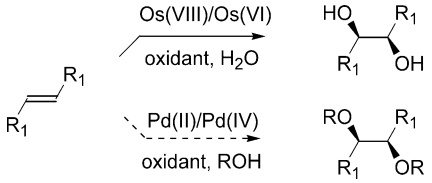
Palladium-catalyzed vicinal oxidation has emerged as an attractive approach for making valuable products from simple and readily available olefins.[1−4] For example, diamination[1b] and aminooxygenation[2] of olefins have been achieved based on the Pd(II)/Pd(IV) catalyst cycle, a mechanistic design that has garnered significant attention as a result of Sanford's efforts.[5] Despite the prevalence of 1,2-dioxygenated motifs in various organic architectures, a corresponding Pd(II)/Pd(IV) dioxygenation of alkenes has not previously been realized. Herein, we report a novel olefin dioxygenation catalyzed by cationic palladium diphosphine complexes. In comparison to related Pd-based methods, this olefin difunctionalization presumably occurs by a distinct Pd(II)/Pd(IV) mechanism and is significantly broad in scope, not limited to terminal olefins and/or alkenes bearing a directing group. Due to the low cost and toxicity of Pd salts relative to Os complexes, this strategy also represents a promising compliment to the well-known Sharpless dihydroxylation (Scheme 1).

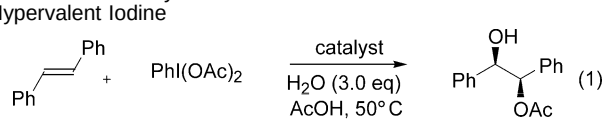
Scheme 1. Proposed Pd(II)/Pd(IV) Compliment to Os(VIII)/Os(VI) Catalytic Dioxygenation of Alkenes



Our initial studies focused on identifying a palladium species capable of catalyzing the desired vicinal oxygenation of *trans*-stilbene (**1**) with hypervalent iodine **2** as the terminal oxidant, in wet acetic acid (eq 1). No background oxidation was observed (Table 1, entry 1). Furthermore, $Pd(OAc)_2$ and $PdCl_2(CH_3CN)_2$ (known catalysts in related Pd-catalyzed aminooxygenations) did *not* promote the vicinal oxygenation (entries 2 and 3). Although the use of diimine ligand 2,2-bipyridine was ineffective (entry 4), a combination of $Pd(OAc)_2$ with BINAP resulted in formation of hydroxyacetate **3**, albeit in low yield (entry 5). In the presence of BINAP, $Pd(TFA)_2$ was found to be a more active catalyst precursor than $Pd(OAc)_2$, affording **3** in improved yield (46%) and 6:1 *syn*:*anti* selectivity (entry 6). Encouraged by the observation that a more non-coordinating counterion appeared to enhance catalyst activity, we investigated the use of cationic complex $[Pd(dppp)(H_2O)_2](OTf)_2$ (**4**).[6] Although cationic Pd species are known to catalyze a range of transformations,[7] to our knowledge, their application in Pd(II)/Pd(IV) reaction pathways has not been explored. Remarkably, 2 mol % of this catalyst efficiently catalyzed the dioxygenation of **1** to afford hydroxyacetate **3** in good yield (72%) and shorter reaction time (2 h at 50 °C).[8]

We were surprised by the selective formation of hydroxyacetate product **3**, in preference to the corresponding diacetate, considering that acetic acid was the solvent. To investigate the origin of the hydroxyl group, we performed an isotopic labeling study using 97% oxygen-18 enriched water. Treatment of *trans*-stilbene (**1**) with 20 equiv of $H_2{}^{18}O$ in anhydrous acetic acid afforded an isotopic mixture of hydroxyacetates **3a**. The relative amounts of unlabeled hydroxyacetate (23.4%), oxygen-18 labeled products (68.3%), and doubly labeled products (8.3%) were determined using mass spectrometry.

Table 1. Pd-Catalyzed Oxidation of *trans*-Stilbene with Hypervalent Iodine



1 **2** **3**

entry	catalyst		mol %	time (h)	yield (%)[a,b]	(*syn*:*anti*)[c]
1	none		none	16	0	
2	$Pd(OAc)_2$		5	16	0	
3	$PdCl_2(MeCN)_2$		5	16	0	
4	$Pd(bpy)(OAc)_2$		5	16	0	
5	$Pd(BINAP)(OAc)_2$		5	16	24	5:1
6	$Pd(BINAP)(TFA)_2$		5	16	46	6:1
7	$[Pd(dppp)(H_2O)_2](OTf)_2$	**4**	2	2	72	6:1

[a] 0.25 mmol scale (0.1 M in HOAc), 1.1 equiv of $PhI(OAc)_2$ and 3.0 equiv of H_2O. [b] Yield by ^1H NMR using internal standard. [c] Determined by ^1H NMR integration.

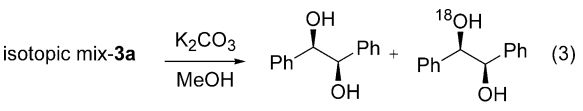
Table 2. Results of Isotopic Labeling Study with ^{18}O-Enriched Water

3a

isotopic mix-**3a**	*m*/*z*[a]	abundance (%)[b]
unlabeled	279.1	23.4
^{18}O-labeled	281.1	68.3
doubly ^{18}O-labeled	283.1	8.3

[a] ESI/MS, $[M + Na]^+$. [b] Integration of peak area.

Hydrolysis of this isotopic mixture of hydroxyacetates **3a** resulted in significant *removal* of the oxygen-18 label. This result demonstrated that the oxygen-18 label was selectively incorporated into the carbonyl of the acetate. Upon treatment with K_2CO_3 and MeOH, unlabeled diol **5a** was observed as the major product (90.3%), along with oxygen-18 labeled diol **5b** (9.7%) (eq 3).[9]



5a (90.3%) **5b** (9.7%)

On the basis of this isotopic labeling study and the *syn* diastereselectivity observed, we propose the mechanism shown in

10.1021/ja711029u CCC: $40.75

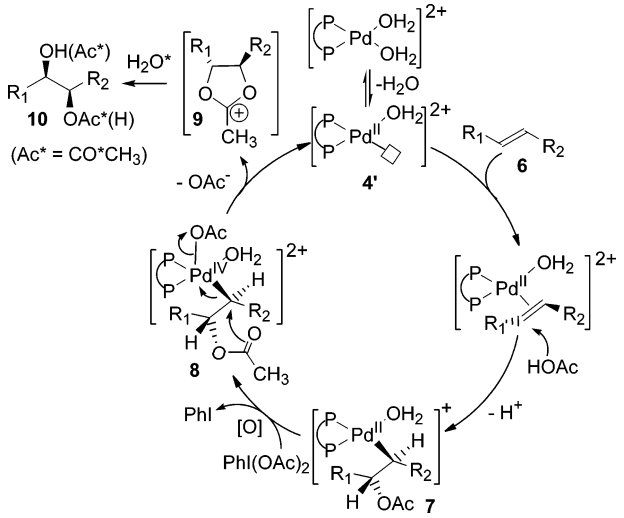
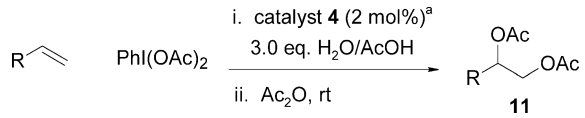


Figure 1. Proposed Pd(II)/(IV)-catalyzed hydroxyacetoxylation.

Table 3. Pd-Catalyzed Diacetoxylation of Representative Terminal Olefins



entry	R	product	temp (°C)	time (h)	yield[b] (%)
1	Ph	**11a**	rt	2	90
2	4-F-Ph	**11b**	rt	3	94
3	4-Cl-Ph	**11c**	rt	2	93
4	3-Cl-Ph	**11d**	rt	6	97
5	$CH_3(CH_2)_7$	**11e**	50	3	81
6	$PhCH_2$	**11f**	50	3	71
7[c]	$BnOCH_2$	**11g**	rt	30	70

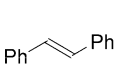
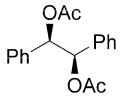
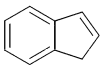
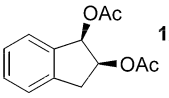
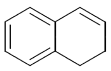
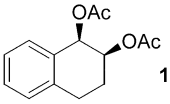
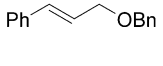
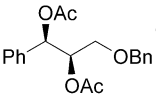
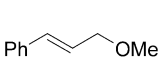
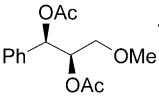
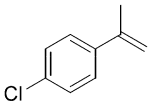
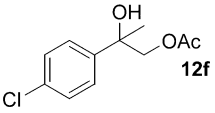
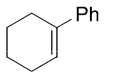
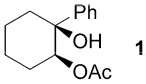
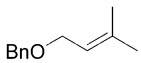
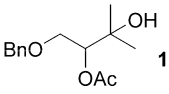
[a] 0.5 mmol scale (0.1 M in AcOH), 2 mol % of catalyst **4**, 1.1 equiv of $PhI(OAc)_2$, and 3.0 equiv of H_2O; then Ac_2O, rt. [b] Isolated yield. [c] 5 mol % of catalyst **4** and 1.5 equiv of $PhI(OAc)_2$ were used.

Figure 1. Cationic Pd complex **4** undergoes *trans*-acetoxypalladation with olefin **6** to provide organopalladium intermediate **7**. In accord with previous mechanistic proposals,[1b,2] oxidation of **7** with hypervalent iodine circumvents β-hydride elimination and generates Pd(IV) intermediate **8**. Intramolecular cyclization forms acetoxonium **9** and regenerates the catalyst via an S_N2-type reductive elimination. Hydrolysis of intermediate **9** delivers the *syn* hydroxyacetate product **10**.

Next, we examined the generality of this novel vicinal oxidation. As shown in Table 3, a number of terminal olefins can be elaborated efficiently. Dioxygenation of styrene initially affords a regioisomeric mixture (ca 1:1) of hydroxyacetate products, in accord with our mechanistic hypothesis. Treatment of the resulting reaction mixture with Ac_2O allowed convenient isolation of diacetate **11a** in 90% yield (entry 1). In comparison to Sigman's dimethoxylation,[3] which is highly effective for phenol derivatives, a complementary class of styrene derivatives is tolerated. Electron-deficient styrene derivatives are functionalized without the requirement of a phenol directing group in excellent yield (greater than 90%, entries 2−4). Moreover, simple aliphatic alkenes, such as 1-decene, allyl benzene, and allyl benzyl ether are diacetoxylated in good yields (entries 5−7).

As shown in Table 4, dioxygenation of 1,2-, and 1,1-disubstituted olefins provides rapid access to products bearing vicinal stereogenic centers with good diastereocontrol. Indene and 1,2-dihydronaphthalene are highly reactive presumably due to their inherent ring

Table 4. Pd-Catalyzed Dioxygenation of Di- and Trisubstituted Olefins

entry	substrate[a]	product	d.r.(*syn*:*anti*)	yield[b] (%)
1		 **12a**	6:1	80
2		 **12b**	10:1	93
3		 **12c**	5:1	95
4		 **12d**	>99:1	76
5		 **12e**	>99:1	66
6[c]		 **12f**	---	70
7[c]		 **12g**	>99:1	83
8[c]		 **12h**	---	61

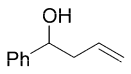
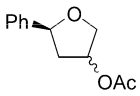
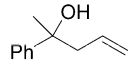
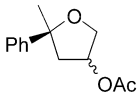
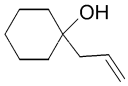
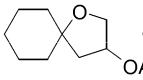
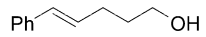
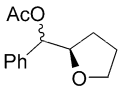
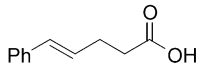
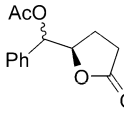
[a] 0.5 mmol scale (0.1 M in HOAc), 2 mol % of catalyst **4**, 1.1 equiv of $PhI(OAc)_2$ and 3.0 equiv of H_2O; then Ac_2O, rt. [b] Isolated yield. [c] No Ac_2O was used.

strain. Diacetates **12b** and **12c** were formed in excellent yields and diastereoselectivity (93% yield, 10:1 dr, entry 2 and 95% yield, 5:1 dr, entry 3). Diacetoxylation of cinnamyl ethers provided the *syn* diacetate products exclusively (76% yield, >99:1 dr, entry 4 and 66% yield, >99:1 dr, entry 5). In analogy to Stahl's aminoacetoxylation of allylic ethers, this high diastereocontrol can be attributed to a more ordered transition state structure due to precoordination of the allylic oxygen to Pd.

Representative 1,1-di- and trisubstituted olefins were oxidized to produce tertiary alcohol products in good yield and with high regioselectivity (entries 6−8). Because tertiary alcohols **12f**, **12g**, and **12h** were formed exclusively, the reaction mixtures were not treated with Ac_2O upon completion. The hydrolysis of acetoxonium ions to provide tertiary alcohols selectively is in accord with Kusumoto's observations.[10] Single-crystal X-ray analysis of **12g** verified that the hydroxy group and the acetate are indeed delivered in a *syn* fashion, as predicted by our mechanistic hypothesis (*syn*:*anti* >99:1, 83% yield, entry 7).

Finally, we would like to report our initial findings on an intramolecular Pd-catalyzed dioxygenations of olefins to construct tetrahydrofurans and lactones, architectures found in many natural products.[11,12] Treatment of 1-phenyl-but-3-en-1-ol with catalyst **4**

Table 5. Intramolecular Pd-Catalyzed Oxidative Tetrahydrofuran and Lactone Ring-Forming Examples

entry	substrate[a]	product		d.r.[b]	yield[c] (%)
1			**13a**	1.1:1	78
2			**13b**	1.1:1	90
3[d]			**13c**	----	80
4			**13d**	2.3:1	90
5[e]			**13e**	1.3:1	85

[a] 0.25 mmol scale (0.1 M in wet HOAc), 1.1 equiv of $PhI(OAc)_2$, 2 mol % of catalyst **4**. [b] Diastereomeric ratio. [c] Isolated yield. [d] 1.5 equiv of $PhI(OAc)_2$ was used. [e] 5 mol % $Pd(TFA)_2$ and 5.5 mol % dppp were used.

in wet AcOH afforded tetrahydrofuran **13a** in good yield as a mixture of diastereoisomers (78% yield, 1.1:1 dr, Table 4, entry 1). Substrates bearing tertiary alcohol groups also underwent 5-*endo* cyclization to generate the corresponding tetrahydrofurans **13b** (90% yield, 1.1:1 dr) and **13c** (80% yield) (entries 2 and 3). As shown in entry 4, 5-phenylpent-4-en-1-ol preferentially undergoes 5-*exo* cyclization to form tetrahydrofuran **13d** regioselectively (90% yield, 2.3:1 dr). By using $Pd(TFA)_2$/dppp as the catalyst, an oxidative lactonization occurred to give cyclic ester **13e** (85% yield, 1.3:1, entry 5). We are currently investigating the use of chiral ligands to improve diastereselectivity and achieve enantiocontrol in these cyclizations.

In summary, we have developed a novel method to dioxygenate alkenes using cationic Pd catalysts. In comparison to related vicinal oxidations, a broad range of olefins can be functionalized in both inter- and intramolecular processes. The catalyst bears two important structural features: an electron-rich diphosphine ligand and non-coordinating counterions. Current studies are underway to elucidate the effect of catalyst structure on the mechanism of this Pd(II)/(IV) dioxygenation.

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Note Added after ASAP Publication. The version of this paper published February 19, 2008, contained an error in Figure 2. The version published on February 22, 2008 has the correct information.

Supporting Information Available: Experimental procedures, spectroscopic data for all new compounds, detailed analysis of the isotopic labeling experiment, and crystallographic data for **12g** in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

References

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