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Dual Role of H_2O_2 in Palladium-Catalyzed Dioxygenation of Terminal Alkenes

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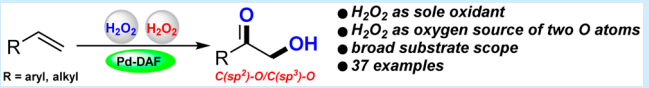
Supporting Information

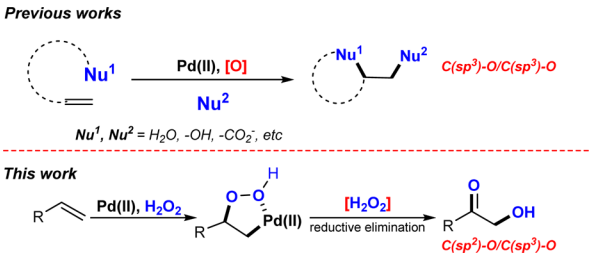
ABSTRACT: A palladium-catalyzed, environmentally friendly dioxygenation reaction of simple alkenes has been developed that enabled rapid assembly of valuable α-hydroxy ketones with high atom economy. Notably, control experiments and ^{18}O isotope-labeling experiments established that H_2O_2 played a dominant dual role in this transformation.



The α-hydroxy ketone moieties have been recognized as privileged structural motifs with diverse biological and medicinal applications[1] and have also found broad use in organic chemistry.[2] As a consequence, many representative methods have been developed for constructing this scaffold from the readily available olefins. Early studies were initiated by RuO_4-catalyzed ketohydroxylation reaction of alkenes with Oxone as oxidant.[3a,b] Recently, Wu's group demonstrated stoichiometric iodine-promoted activation and oxidation of alkenes to synthesize α-hydroxy ketones.[3c] Thus, the development of an efficient and environmentally benign process is still highly appealing and in demand.

The dioxygenation of alkenes has emerged as one of the most attractive and powerful strategies for efficient construction of two C−O bonds with maximal atom and step economy in recent years. Since Sharpless' seminal discovery of asymmetric dihydroxylation of alkenes via a ligand-accelerated process, extensive efforts have been devoted to develop efficient methods for this type of transformation.[4] In this regard, palladium-catalyzed dioxygenation of alkenes has become one of the most attractive and fascinating areas in contemporary organic synthesis.[5] In general, the chemical conversion was triggered by oxypalladation (Wacker-type process),[6] and then the high-valent Pd intermediates were generated under an oxidant such as hypervalent iodine reagents,[5a,b] nitrite,[5c,d] peroxy acid,[5e] and molecular oxygen,[5f,h] etc., which released the products with two newly formed $C(sp^3)$−O bonds at last (Scheme 1).[7] Most notably, applying the environmentally benign oxidants is the persistent goal for synthetic chemists.[8,9] Representatively, our group successfully developed the first example of Pd-catalyzed diacetoxylation of alkenes using molecular oxygen as the sole oxidant, which opens up a new sight for the green synthesis.[5f] On the other hand, the Liu group has comprehensively reported Pd-catalyzed chloroamination and oxyamination of alkenes by "green" H_2O_2 as the oxidant.[10] Inspired by the aforementioned background and our longstanding interest in Pd-catalyzed difunctionization of olefins,[11] we disclose herein a Pd-catalyzed dioxygenation of alkenes to construct α-hydroxy ketones with H_2O_2 as oxidant and oxygen source. Remarkably, the H_2O_2 played two distinguished roles to afford $C(sp^2)$−O and $C(sp^3)$−O bond formations across the reaction.

Scheme 1. Pd-Catalyzed Dioxygenation of Alkenes



We initiated the investigation using 4-*tert*-butylstyrene as substrate in the presence of 7.5 mol % of $Pd(OAc)_2$ and 3.0 equiv of H_2O_2 in AcOH at room temperature, which afforded α-hydroxy ketone **2c** in 5% yield (Table 1, entry 1). However, α-acetate ketone **3c** was the major product. Next, the use of cosolvents showed little improvement in the efficiency, and AcOH was unnecessary for the formation of **2c** (Table 1, entries 2−4, 8). In regard to acidic additives, compared with 10-camphorsulfonic acid (10-CSA) and trifluoromethanesulfonic acid (TfOH), the addition of trifluoroacetic acid (TFA) obviously increased the selectivity and yield (Table 1, entries 5−7). To suppress the mono-oxidative side reaction (Wacker product), a series of bidentate *N*-containing ligands were screened. The reaction was almost completely inhibited at room temperature when **L1** (bpy) was added, which only gave the desired product in 9% yield, and 90% of the starting material **1c** was recovered simultaneously (Table 1, entry 9). Elevating the reaction temperature exhibited exciting results, which afforded the desired product **2c** in 65% yield at 75 °C (Table 1, entries 10 and 11). Further examination of other ligands such as 1,10-phenanthroline (phen, **L2**), diazafluorenone (DAF, **L3**), and dipyridinyl ketone (dpk, **L4**) proved

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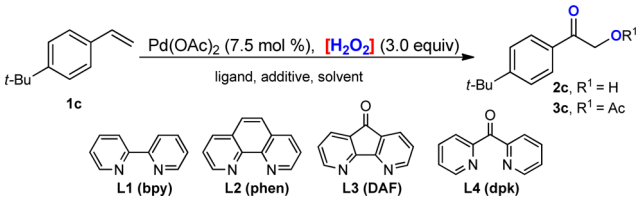
Table 1. Optimization of Reaction Conditions[a]



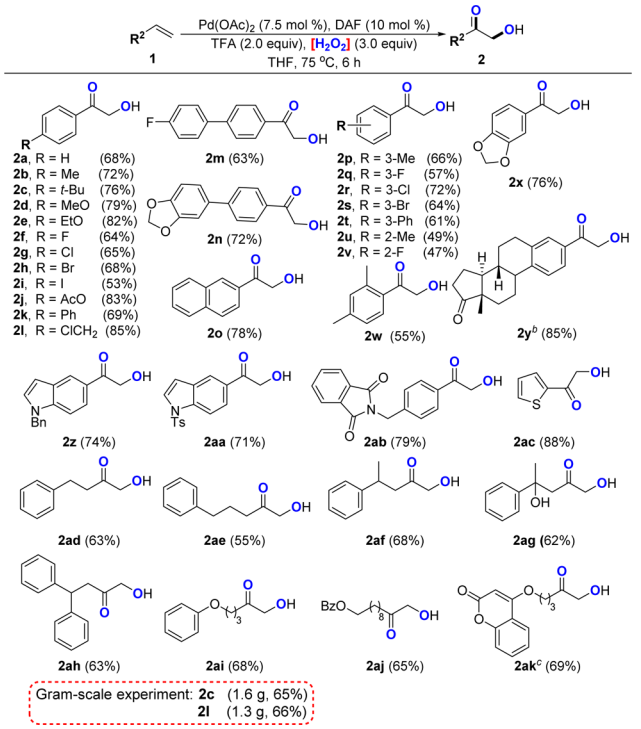
entry	additive	L	solvent (v/v)	temp (°C)	yield[b] (%) 2c	3c
1			AcOH	rt	5	15
2			AcOH/CH_3CN (1/1)	rt	ND	16
3			AcOH/CH_3NO_2 (1/1)	rt	trace	15
4			AcOH/THF (1/1)	rt	15	13
5	TFA		AcOH/THF (1/1)	rt	34	5
6	10-CSA		AcOH/THF (1/1)	rt	ND	ND
7	TfOH		AcOH/THF (1/1)	rt	ND	ND
8	TFA		THF	rt	43	ND
9	TFA	**L1**	THF	rt	8	ND
10	TFA	**L1**	THF	50	50	ND
11	TFA	**L1**	THF	75	65	ND
12	TFA	**L2**	THF	75	60	ND
13	TFA	**L3**	THF	75	**80 (76)**[c]	ND
14	TFA	**L4**	THF	75	74 (73)	ND

[a]Reaction conditions: **1c** (0.3 mmol), $Pd(OAc)_2$ (7.5 mol %), H_2O_2 (3.0 equiv), solvent (1.0 mL) with sealed tube for 6 h; additives (2.0 equiv) were added; **L** (10 mol %) was added; ND = not detected. [b]Yields determined by GC with *n*-dodecane as internal standard. [c]Isolated yield is in the parentheses.

that **L3** was most suitable for the transformation (Table 1, entries 12−14). On the basis of the above results, the optimal reaction conditions for this dioxygenation process are $Pd(OAc)_2$ (7.5 mol %), DAF (10 mol %), H_2O_2 (3.0 equiv) in THF at 75 °C for 6 h (see the Supporting Information (SI) for details).

With satisfactory conditions in hand, we examined the scope of the dioxygenation reaction by testing a series of terminal alkene substrates containing various substitution patterns and diverse functional groups. Moderate to good yields were obtained when a broad range of electron-rich styrenes were employed (**2b−e,j,l,n**) (Scheme 2). Electron-poor styrenes were also successfully converted to the desired products with acceptable isolated yields (**2f−i**) (Scheme 2). *Ortho*-substituted styrenes were transferred to the target products with obviously lower yields than those of the *para*- and *meta*-substituted styrenes (**2u−w**) (Scheme 2), which might be due to the steric hindrance. In addition, more complex substrate **1y** was compatible under the standard conditions and provided the desired product **2y** in 85% yield. Notably, the heteroaromatic substrates successfully converted into the corresponding α-hydroxy ketones (**2z−ac**) (Scheme 2). Gratifyingly, non-activated olefins were also able to afford the products in moderate yields (**2ad−ak**) (Scheme 2). Moreover, *tert*-hydroxy could be observed under the acidic conditions (Scheme 2, **2ag**). Specifically, **2c** and **2l** could be obtained in 65% and 66% yields in a gram-scale experiment. The products **2af** and **2ag** emitted the smell of cumin, which may have a latent application value for spices.[12]

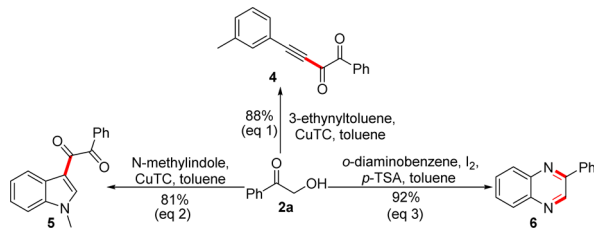
Scheme 2. Pd-Catalyzed Dioxygenation of Alkenes[a]



[a]Reaction conditions: olefins **1** (0.30 mmol), $Pd(OAc)_2$ (7.5 mol %), DAF (10 mol %), TFA (2.0 equiv), H_2O_2 (3.0 equiv) in THF (0.15 M) with sealed tube at 75 °C for 6 h, isolated yield. [b]On 0.10 mmol scale. [c]On 0.20 mmol scale.

Subsequently, in view of the importance of α-hydroxy ketone in organic synthesis, a series of further transformations of product **2a** were carried out as shown in Scheme 3. For example, the Cu-catalyzed one-pot approach toward ynedione **4**, which is a powerful synthetic building block for specific heterocycles, has been achieved with good yield (Scheme 3, eq 1). The C3-dicarbonylation of indoles was also realized under the treatment of CuTC (Scheme 3, eq 2). Moreover, a potentially bioactive 2-phenylquinoxaline skeleton **6** could be prepared from **2a** via a metal-free catalysis method in 92% yield (Scheme 3, eq 3).

Scheme 3. Selected Transformations of 2a[a]



[a]Reaction conditions: see the SI for details.

To gain a better understanding of this transformation, some control experiments were conducted. Under the standard conditions, no desired product was detected in the oxidation of possible reaction intermediates such as 1-phenylethane-1,2-diol **7** and acetophenone **8** (Scheme 4).[13] Thus, we postulated that the plausible pathway involved the formation of peroxide, which went through nucleophilic attack by hydrogen peroxide

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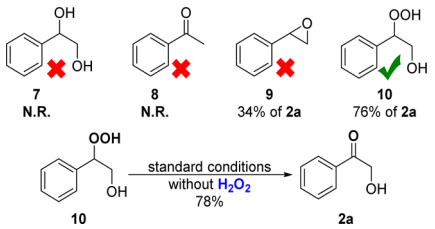
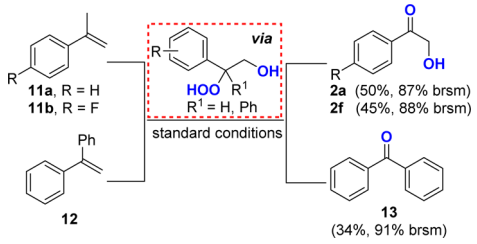
Scheme 4. Control Experiments



on the carbon of epoxide or C=C bond. We found that the epoxide **9** and hydroxyperoxy alcohol **10**[14] converted into the product **2a** under the standard reaction conditions, with 34% and 76% yields, respectively. Furthermore, compound **10** could transfer to **2a** in the absence of H_2O_2. Therefore, neither compounds **7** and **8** nor the epoxide **9** were possible intermediates, as **9** exhibited lower yield and a more complex system than that of styrene.

In order to further verify our hypothesis, we treated the disubstituted terminal olefins with standard conditions. The reactions of α-methylstyrenes (**11a**, **11b**) (Scheme 5) could

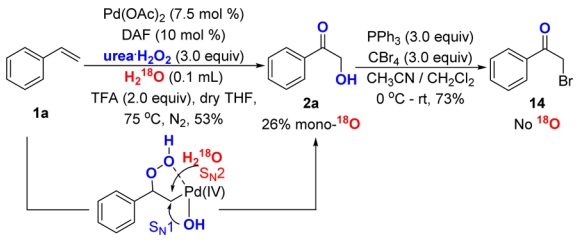
Scheme 5. Disubstituted Terminal Olefins under Standard Conditions



also proceed smoothly to provide the corresponding α-hydroxy ketones. Meanwhile, 1,1-diphenylethene **12** could be converted to benzophenone **13** under the optimized conditions, albeit with somewhat reduced yield. All of these results suggested that hydroxyperoxide intermediates might be possible intermediates in this chemical process.

Next, the isotope-labeling experiments were performed. When urea/H_2O_2 and $H_2{}^{18}O$ were used instead of H_2O_2 aq under the standard conditions, product **2a** with 26% mono-^{18}O label was detected by HRMS-ESI (Scheme 6) (see the SI for

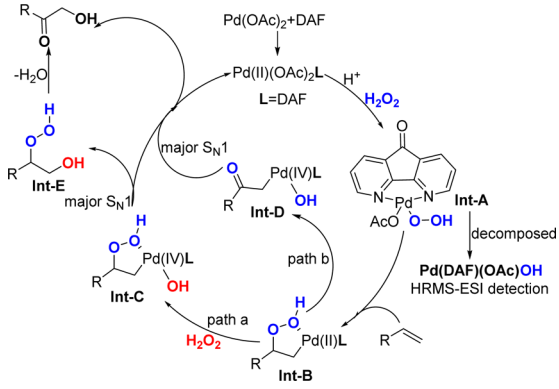
Scheme 6. ^{18}O-Labeling Experiments



details). Interestingly, **2a** was transferred to α-bromo ketone **14** without ^{18}O incorporation. Hence, it is supposed that the oxygen atoms of carbonyl and hydroxyl were derived from H_2O_2. Notably, the palladium(IV) complex might be involved in the formation of C−OH bond via the direct reductive elimination (S_N1 type nucleophilic attack) as a major pathway.

On the basis of above results and literature precedents, we postulate a tentative mechanism for the dioxygenation of alkenes in Scheme 7. Initially, $Pd(OAc)_2$ coordinates with

Scheme 7. Tentative Mechanism



ligand DAF. The Pd(II)/DAF complex was then oxidized by H_2O_2 to generate the key peroxy Pd complex **Int-A**,[15] in which acid would promote the dissociation of OAc^- from the palladium center. Next, *cis*-oxypalladation of alkene produced the alkylpalladium species **Int-B**, which is consistent with the effect of steric hindrance.[16] The transient 5-membered Pd(II) **Int-B** could be oxidized to the corresponding Pd(IV) **Int-C** by a second molecular of H_2O_2, followed by reductive elimination to release hydroxyperoxide **Int-E**.[17] Dehydration of **Int-E** occurs to give the α-hydroxy ketone product. In the other scenario, **Int-B** converts into α-ketone alkyl-Pd(IV) **Int-D** by the oxidation of the intramolecular peroxy bond, which transfers directly to α-hydroxy ketone by natural reductive elimination. Additionally, we detected Pd(DAF) (OAc)OH by HRMS-ESI, which should be decomposed from **Int-A** (see the SI for details).

In summary, a novel and practical Pd-catalyzed dioxygenation of alkenes has been developed. In addition, the dioxygenation reaction presents a method of utilizing H_2O_2 as the oxidant and the oxygen source. As a result, the α-hydroxy ketones could be prepared from readily available raw materials, which will inspire new designs of the difunctionalization of alkenes. Further mechanistic studies, the scope of the reaction, and the further difunctionalization reaction of alkenes using green oxidants are in process in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01228.

Experimental procedures, condition screening table, characterization data, and NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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