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Aerobic Acetoxyhydroxylation of Alkenes Co-catalyzed by Organic Nitrite and Palladium

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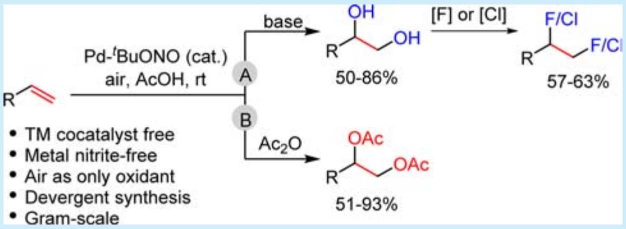
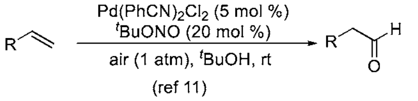
Ⓢ *Supporting Information*

ABSTRACT: An aerobic acetoxyhydroxylation of alkenes cooperatively catalyzed by organic nitrite and palladium at room temperature using clean and cheap air as the sole oxidant has been developed. Various vicinal diols, diacetoxyalkanes, and dihalogenoalkanes have been synthesized. The gram-scale synthesis has also been approached. Vicinal difluorination and dichlorolation products have also been achieved via this reaction.



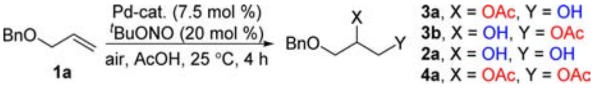
Among oxidative functionalizations of alkenes, dihydroxylation is an important access to vicinal diols that is usually approached by one-step Upjohn reaction[1a] and its asymmetric version Sharpless dihydroxylation,[1b] two-step Prévost−Woodward reaction,[2] and ring opening of epoxides. As drawbacks, very toxic and expensive OsO_4 or stoichiometric silver carbonates are used in Upjohn or Prévost−Woodward reactions, respectively. Recently, great progress has been achieved for the dihydroxylation reaction under osmium-free conditions.[3−7] In addition to transition-metal catalysis, the proton-catalyzed diacetoxylation of alkenes using hypervalent iodane reagents or peracids has been reported.[3] A diacetoxylation of alkenes with $Pd/Cu/AgNO_2$ as the co-catalytic system has been reported recently.[4] After the pioneering work on Pd-catalyzed aerobic dioxygenation of alkenes,[5] the reaction mechanism was discussed decades ago.[8] In all cases, the NO_x species plays key role in Pd−NO-catalyzed aerobic processes.[9,10] Previously, we have reported an anti-Markovnikov−Wacker oxidation using ᵗBuONO as a redox co-catalyst (eq 1).[11,12] Herein, we have extended this catalytic system to a synthetically practical acetoxyhydroxylation of alkenes with air at room temperature, providing a divergent access to diols and diacetoxyalkanes.


(1)

Initially, the reaction conditions of acetoxyhydroxylation of **1a** co-catalyzed by Pd and ᵗBuONO have been investigated. Acetoxyhydroxylation products **3a** and **3b** were obtained in 53% total yield (Table 1, entry 1). $Pd(CH_3CN)_2(NO_2)_2$ without ᵗBuONO afforded **3** in low yields (entry 3). The reaction in the absence of oxygen gave only 7% yield (entry 7).

Acetoxyhydroxylation intermediates are divergent precursors of vicinal diol **2a** or diacetoxyalkane **4a**.[2] With hydrolysis or acetylation workup, either **2a** and **4a** was obtained in 55% and 51% yields, respectively (entries 11 and 12). The standard conditions for a divergent access to diols and diacetoxyalkanes have been established with 7.5 mol % of $Pd(CH_3CN)_2Cl_2$, 20 mol % of ᵗBuONO, 1 atm of air, at 25 °C with hydrolysis (conditions A) or acetylation (conditions B) workup.

Table 1. Reaction Conditions[a]



entry	Pd cat.	other conditions	3^{b} (%)
1	$Pd(CH_3CN)_2Cl_2$	none	53[c]
2	$Pd(CH_3CN)_2Cl_2$	with O_2	52
3	$Pd(CH_3CN)_2(NO_2)_2$	no ᵗBuONO	12
4	$Pd(PhCN)_2Cl_2$	none	49
5	$PdCl_2$	none	38
6	$Pd(OAc)_2$	none	8
7	$Pd(CH_3CN)_2Cl_2$	under argon	7
8	$Pd(CH_3CN)_2Cl_2$	2.5 mol % [Pd]	35
9	$Pd(CH_3CN)_2Cl_2$	ᵗBuONO 7.5%	28
10	$Pd(CH_3CN)_2Cl_2$	ᵗBuONO 20%	53
11[d]	$Pd(CH_3CN)_2Cl_2$	K_2CO_3, MeOH	55 (**2a**)
12[e]	$Pd(CH_3CN)_2Cl_2$	Ac_2O, 50 °C	51 (**4a**)

[a] Conditions: **1a** (0.5 mmol), cat. (7.5 mol %), ᵗBuONO (20 mol %), AcOH (5 mL), 25 °C, air (1 atm), 4 h. [b] Combined yields of **3a** and **3b**, no **2a** or **4a** observed. Determined by ^1H NMR with an internal standard ($PhCH_2CH_2CO_2Et$). [c] **3a**/**3b** = 21/32 with BnOH decomposed from **1a**. [d] Worked up with K_2CO_3 (conditions A). [e] Worked up with Ac_2O (condition B).

Under the standard conditions A, a variety of vicinal diols were obtained in generally good yields (Scheme 1). A wide range of functional groups tolerate the reaction conditions. For example, 10-undecenoic acid **1h** without a protecting group was subjected to the dihydroxylation conditions to give the desired diol **2h** in 84% yield at room temperature. The dihydroxylation of Weinreb amide **1k** afforded the corresponding

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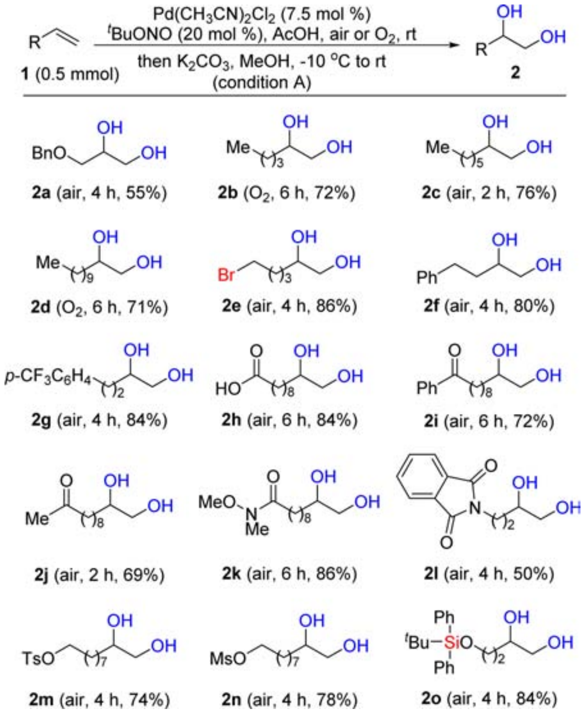
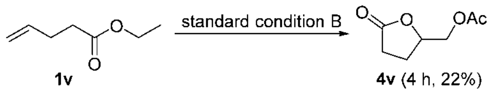
Scheme 1. Dihydroxylation of Alkenes



diol **2k** in 86% yield. Other functional groups or protecting groups such as benzyloxy, bromo, TBDPS, carbonyl, and sulfonyl groups have all survived and provided target diols in good to high yields (**2a**, **2e**, **2i**, **2j**, **2m**, **2n**, and **2o**). With respect to the nonfunctionalized alkenes such as 1-hexene, 1-octene, and 1-dodecene, the desired diols could also been obtained in good yields (**2b**−**d**).

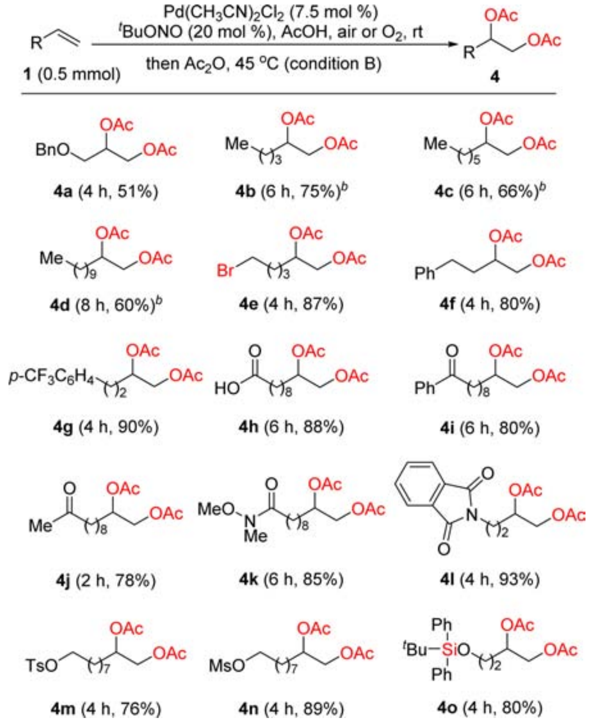
Under the standard conditions B, the palladium-catalyzed diacetoxylation of various alkenes **1** affords the corresponding products in generally good yields (Scheme 2). Compared to the dihydroxylation reaction demonstrated in the middle column of Scheme 2, similar yields were given with the same acetoxyhydroxylation intermediates. Various functional groups or protecting groups tolerate the reaction conditions. For example, diacetoxylation products **4h** and **4k** were obtained from the corresponding unsaturated carboxylic acid **1h** and Weinreb amid **1k** in 88% and 85% yields, respectively. The alkenes bearing benzyloxy, bromo, and sulfonyl groups and TBDPS could also survive under standard conditions B to provide the desired products in good to high yields (**4a**, **4e**, **4m**, **4n**, and **4o**). Phthalimidyl butene gave corresponding diacetoxylation product **4l** in high yield.

This reaction has the limitation on the alkenes with conjunctive electron-withdrawing groups as well as internal alkenes. The substrates listed in Figure 1 gave trace products. Cyclohexene **1p** gave cyclohex-2-en-1-one as the major product. Styrene and methyl acrylate **1t** partially polymerized during the reaction. With respect to the intramolecular reaction, cyclization product **4v** was afforded from ethyl pent-4-enoate **1v**, although the yield was only 22% (eq 2).



(2)

Scheme 2. Diacetoxylation from Alkenes



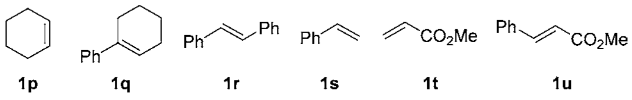
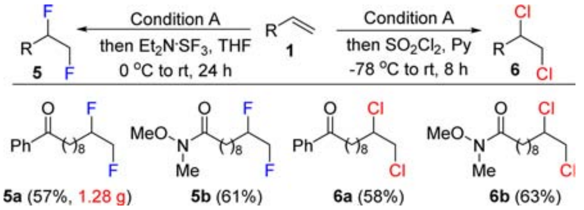


Figure 1. Unsuccessful substrates.

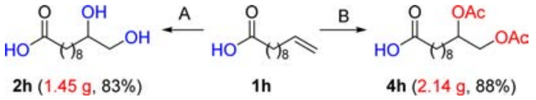
Alkenes **1** are good precursors for vicinal difluorides or dichlorides. Difluorination of diols **2** with DAST (Et_2NSF_3) afforded vicinal difluorides **5a** and **5b** in 57% and 61% yields, respectively (Scheme 3). Vicinal dichlorides **6a** and **6b** were obtained with thionyl chloride in acceptable yields.

Scheme 3. Dihalogenation of Alkenes



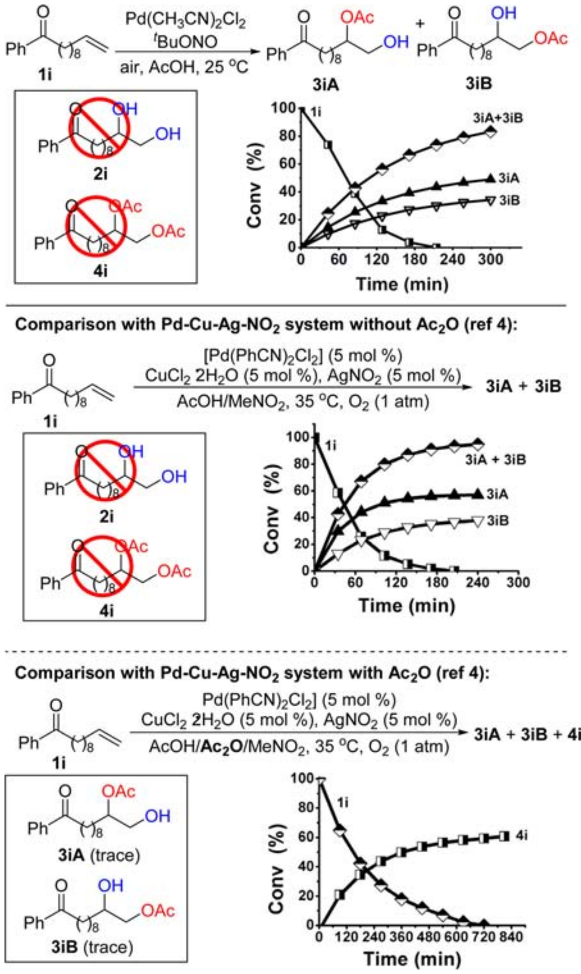
This reaction can be scaled up to gram scale. For example, 10-undecenoic acid **1h** was subjected to both dihydroxylation and diacetoxylation conditions, and the corresponding diol **2h** and diacetoxyl acid **4h**respectively, were obtained in high yields (Scheme 4).

Scheme 4. Gram-Scale Synthesis



In the ^1H NMR monitoring experiment, the formation of acetoxyhydroxylation products **3iA** and **3iB** was observed (Scheme 5, top). Similar results were given under the Grubbs conditions[4] without acetyl anhydride. The reaction in the

Scheme 5. NMR Monitoring Experiments



presence of Ac_2O under Grubbs conditions gave **4i** as the major product, probably due to the result of acetylization of mono-acetoxyl intermediates **3i**. Therefore, we believe similar reaction pathways must be involved for both cases.

Using the acetoxyhydroxylation reaction of **1a** to **3a** and **3b** as the model reaction, the kinetic study was performed to investigate the effects of the catalyst and reagents. A first-order dependence or initial rate on the amount of $Pd(CH_3CN)_2Cl_2$ was established (Figure 2A), suggesting Pd(II) should be the catalytically active species in this reaction. The zeroth-order dependence on [**1a**] or [^{t}BuONO] suggests that neither alkene **1a** nor ^{t}BuONO participates in the rate-determining step (Figure 2B,C). Thus, NO and its oxidation form NO_2 should not bind on the Pd center to work as a whole to participate in the rate-determining step.

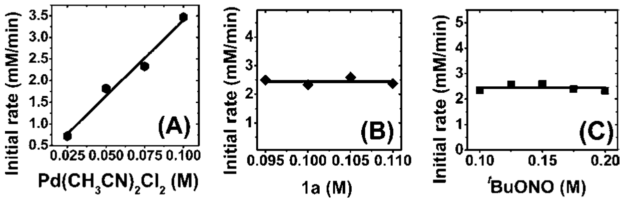
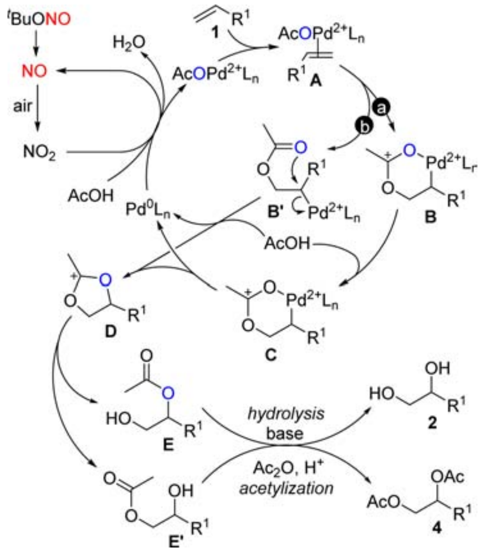
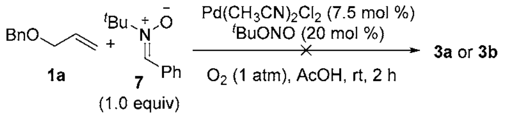


Figure 2. Dependence of the initial rate on (A) first-order dependence on [$Pd(CH_3CN)_2Cl_2$], (B) zeroth-order dependence on [**1a**], and (C) zeroth-order dependence on [^{t}BuONO].

A plausible mechanism was proposed on the basis of monitoring experiments and kinetic study (Scheme 6). AcOH attacks complex **A** to generate either **B** or **B′**, followed by release of Pd^0 through the formation of intermediate **D**. Rearrangement of **D** affords acetoxyhydroxylation isomers **E** and **E′**, which is supported by the ^{1}H NMR monitoring experiment in Scheme 6. Compound **E** is further hydrolyzed to diol **2**, and **E′** is acetylated to diacetoxylation product **4**. The catalytically active Pd(II) species is regenerated by the oxidation by NO_2, which is regenerated from the oxidation of NO with O_2 (air). The use of a radical could be supported by a radical-trapping experiment (eq 3).[13]

Scheme 6. Proposed Mechanism





(3)

In conclusion, we have developed a direct acetoxyhydroxylation of alkenes cooperatively catalyzed by ^{t}BuONO and palladium using clean and cheap air as the sole oxidant at room temperature, providing a divergent access to various vicinal diols, diacetoxyalkanes, and dihalogenoalkanes. As a synthetically practical method, gram-scale synthesis has also been provided. Vicinal difluorination and dichlorolation products could be achieved via this reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02743.

> Experimental details and spectroscopic data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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