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Palladium-Catalyzed Oxime Assisted Intramolecular Dioxygenation of Alkenes with 1 atm of Air as the Sole Oxidant

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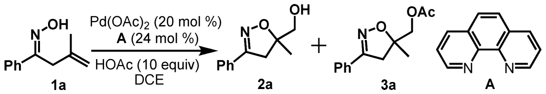
Palladium-mediated organic transformations continue to be a fascinating area in organic synthesis as well as organometallic chemistry due to their versatility and ability to give unexpected outcomes.[1] Among them, palladium-catalyzed difunctionalization of alkenes has attracted much attention.[2,3] Recently, palladium-catalyzed dioxygenation[3] of alkenes has emerged as an alternative approach to the synthesis of vicinal diols, which were previously prepared by Sharpless dihydroxylations.[4] While significant success had been achieved, co-oxidants such as BQ, $PhI(OAc)_2$, and Ag(I) as well as Cu(II) salts are necessary for the catalytic cycle. Although Jiang and co-workers employed molecular O_2 as the sole oxidant, high pressure and temperature are required.[3d] Atmospheric oxygen should be an ideal source of oxygen in terms of environmental benignity, offering both economical and practical advantages. However, using atmospheric oxygen as the sole oxidant without any other co-oxidants still remains a tremendous challenge in this field.[5] Herein, we present the first palladium-catalyzed oxime assisted intramolecular dioxygenation of akenes with 1 atm of air as the sole oxidant under very mild conditions.

Very recently, our group has embarked upon the palladium-catalyzed functionalization of alkenes.[6] Controlled β-hydride elimination in transition-metal-catalyzed reactions is an efficient strategy for further elaboration of the newly formed metal complex. Based on our previous work together with inspiration from Sigman's work,[3a,b] we hypothesized that it may be possible to combine intramolecular nucleopalladation and reductive elimination, while retarding β-hydride elimination, to realize a palladium-catalyzed dioxygenation of alkene by rational design of substrate.[5c,7] Owing to the coordinating ability and easy cleavage of the N−O bond and the versatility of the resulting product,[8] initially we chose (*Z*)-oxime **1a** containing a strategically positioned disubstituted terminal alkene as the substrate for our model study.

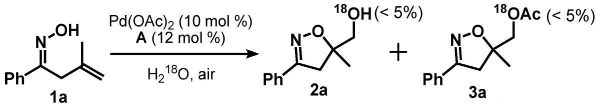
Table 1. Optimization Studies[a]



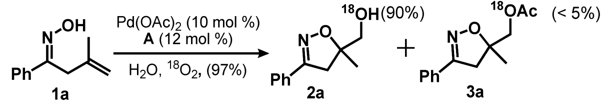
entry	oxidant	*T* (°C)	time (h)	yield (**2a**/**3a**) (%)[b]
1	O_2	25	8	70 (66:34)
2	$PhI(OAc)_2$	25	24	35 (55:45)
3	$Cu(OAc)_2$	25	24	trace
4	BQ	25	24	trace
5	air	25	18	73 (64:36)
6	-	25	24	trace
7	air	40	18	74 (60:40)
8[c]	air	40	24	75 (55:45)
9[d]	air	40	48	66 (58:42)
10[c,e]	air	40	24	78 (53:47)
11[f]	air	40	24	52 (56:44)

[a] Unless noted otherwise, the reactions were carried out on a 0.30 mmol scale of **1a** with 10 equiv of HOAc (3 mmol), 24 mol % of ligand **A** (0.072 mmol), and 20 mol % of $Pd(OAc)_2$ (0.06 mmol) in 1,2-dichloroethane (DCE). [b] Isolated yield, the ratio of **2a**/**3a** was determined by crude ^1H NMR. [c] 10 mol % of $Pd(OAc)_2$ were used. [d] 5 mol % of $Pd(OAc)_2$ were used. [e] 15 equiv of H_2O were added. [f] 0.2 g of 4 Å MS was added.

To our delight, when **1a** was treated with 20 mol % $Pd(OAc)_2$, 24 mol % ligand **A** (1,10-phenanthroline), and 10 equiv of HOAc, dioxygenation of olefin indeed proceeded readily under 1 atm of molecular O_2 at room temperature to give the dioxygenated products **2a** and **3a** in satisfactory yield (Table 1, entry 1). The ligand used has a significant effect on the efficiency of this reaction and **A** was found to be the best ligand (for details of ligands screening, see Supporting Information). Other oxidants were also examined, and it is notable that 1 atm of air proved to be the best choice in terms of reaction efficiency, as well as practical and economical factors (Table 1, entries 1−5). We also observed that a small amount of water is favorable to this reaction (Table 1, entries 8, 10, and 11). Finally, we found that, under 1 atm of air, 10 mol % $Pd(OAc)_2$, 12 mol % ligand **A**, 10 equiv of HOAc, and 15 equiv of H_2O afforded the dioxygenated product with the highest yield (Table 1, entry 10). The catalyst loading of $Pd(OAc)_2$ could be further lowered to 5 mol % to give the desired products with a slightly lower yield (Table 1, entry 9).



(1)



(2)

The presence of molecular oxygen is crucial for the reaction (Table 1, entries 2−4). Control experiments showed that **2a** and **3a** are not interconvertible under the reaction conditions. To investigate the origin of the hydroxyl group of **2a**, isotopic labeling studies with $H_2{}^{18}O$ and $^{18}O_2$ were performed (eqs 1 and 2). The isotopic labeling studies demonstrated clearly that the oxygen of the hydroxyl group of **2a** originated from molecular O_2, hence offering incorporation of the later into synthetically useful product under mild conditions.

Next, we examined the generality of this methodology, and the results are summarized in Table 2.[9] With factors such as easy removal of the acetyl group and practical convenience considered, the initially formed mixtures of alcohol and ester were treated with K_2CO_3 in methanol directly to give the alcohol exclusively. As shown in Table 2, the substituents on the oxime moiety have no significant influence on the efficiency of this reaction. Both aromatic and aliphatic groups were tolerated and furnished the target products in comparable yields. The introduction of heterocycles into this system makes this methodology more useful for the preparation of pharmaceuticals and agrochemicals (Table 2, **2e** and **2f**). Addition of one methyl group to the tether CH_2 has no detrimental effect on the reaction efficiency (Table 2, **2j**). However, two methyl groups or a bulky phenyl group on the tether CH_2 resulted in lower yields (Table 2, **2m** and **2n**). Notably, the dioxygenation proceeded smoothly even for the alkene conjugated with oxime (Table 2, **2o**

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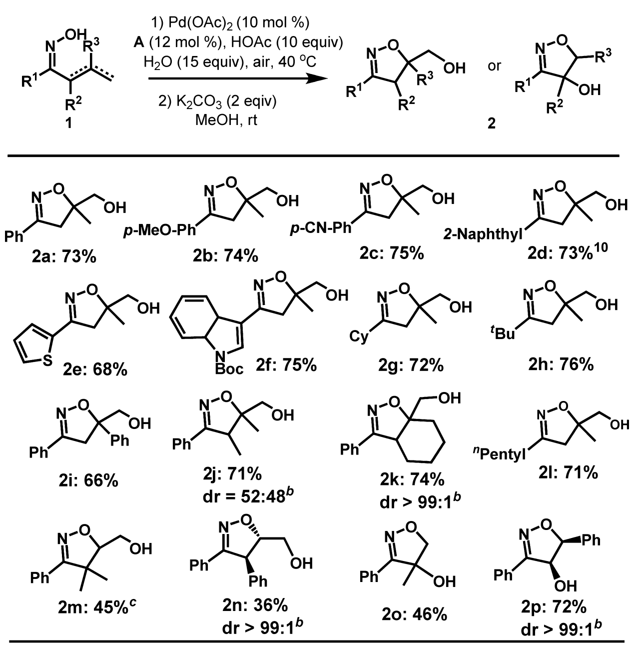
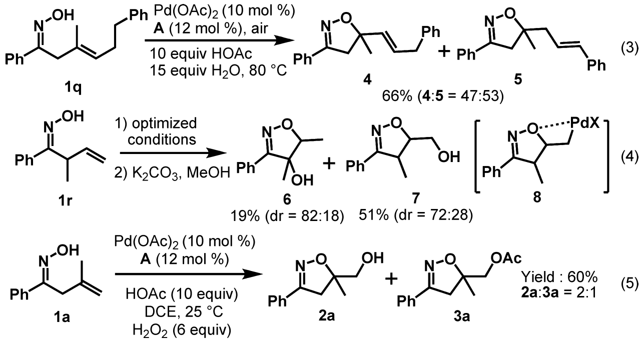
Table 2. Pd-Catalyzed Oxime Assisted Intramolecular Dioxygenation of Alkenes with 1 atm of Air as the Sole Oxidant[a]



[a] The reactions were carried out on a 0.3 mmol scale of **1** with 10 equiv of HOAc (3 mmol), 10 mol % of $Pd(OAc)_2$ (0.03 mmol), 12 mol % ligand **A** (1,10-phenanthroline), and 15 equiv of water in 1,2-dichloroethane (DCE), under 1 atm of air atmosphere. [b] The ratio of diastereomers was determined by crude ^{1}H NMR. [c] 21% of *E* isomer of the starting material was recovered (the *E* isomer is a very poor substrate for this reaction).

and **2p**). In addition, the rigid alkene also could be used as a substrate with good diastereoselectivity and yield (Table 2, **2k**).

To probe the mechanism of this reaction, substrates **1q** and **1r**, both of which contain a β-proton after hydroxyl-palladation, were designed and subjected to the standard conditions. As expected, no dioxygenated product was observed for **1q** (eq 3). Only β-hydride elimination product **4**, accompanied by its double bond isomer **5**, was produced in 66% yield with a ratio of 47:53. This indicates that the intramolecular cyclization was followed by β-hydride elimination to give olefin **4** which isomerized to **5** easily under the reaction conditions. To our surprise, a mixture of dioxygenated products (**6** and **7**) from **1r** was obtained while no β-hydride elimination product was detected when **1r** was subjected to the reaction conditions (eq 4). We reasoned that the coordination of oxygen to palladium in the metal complex **8** may have prohibited the *syn* β-hydride elimination. These experiments demonstrated the existence of a palladium-alkyl intermediate **8**. The absence of substituent at the 2-position of the terminal alkene led to allylic isomerized product **6**, which illustrates that the substituent at the 2-position of the terminal alkene is important to retard the 1,3-isomerization of allylic palladium complex.[11] There was no reaction when **1a** was treated with stoichiometric $Pd(OAc)_2$ in the absence of air or O_2, a condition under which **3a** should be formed exclusively according to Wacker oxidation mechanism.[12] Therefore, this reaction is not a simple variant of the Wacker oxidation. When H_2O_2 was used as oxidant, similar results with oxygen were observed (eq 5). Furthermore, the reductive elimination of palladium-alkyl complex to form a C−O bond is mainly observed in $Pd^{II/IV}$ catalyzed organic transformations.[2b,d,f,3d,5f] On the basis of these experimental results, we assumed that the $Pd^{II/IV}$ catalysis might be involved in this reaction.



In conclusion, we have developed a palladium-catalyzed oxime assisted intramolecular dioxygenation of alkenes by using 1 atm of air as the sole oxidant. This methodology incorporated atmospheric O_2 into synthetically useful compounds efficiently under extremely mild conditions, which make it environmentally benign, economical, and practical. Further study toward the mechanism and development of an asymmetric version is in progress in our laboratory.

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Supporting Information Available: Additional experimental procedures, all chromatograms, and spectral data for reactions products. This material is available free of charge via the Internet at http://pubs.acs.org.

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