ORGANIC LETTERS

2010
Vol. 12, No. 20
4482−4485

Palladium-Catalyzed Tandem Diperoxidation/C−H Activation Resulting in Diperoxy-oxindole in Air

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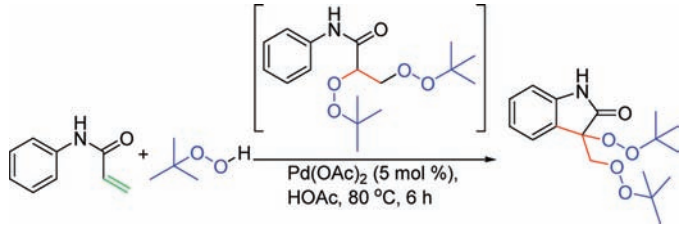
Received July 19, 2010

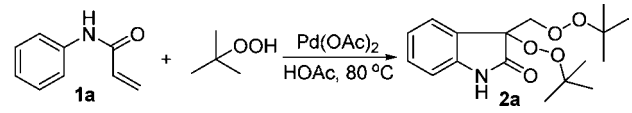
ABSTRACT



A highly efficient and facile palladium-catalyzed tandem diperoxidation and C−H activation process was reported, which provides a new pathway for the synthesis of biologically active diperoxides as well as oxindole derivatives from readily available starting materials in excellent chemical yields.

Peroxides are a privileged structural motif found in many important natural products and pharmaceutical agents, which show antitumor, anticancer, and antiparasite activities.[1] Artemisinin is an efficient antimalarial medicine with the essential peroxide unit for its high antimalarial potency.[2] However, the development for the synthesis of the peroxides still remains challenging, especially for diperoxides.[3] To date, there has been only one report that mentioned the transition-metal-catalyzed diperoxidation of olefin under basic conditions.[4] In this communication, we report a new palladium-catalyzed tandem process, including diperoxidation of olefins and C−H activation under acidic conditions, which generates diperoxy-oxindoles (Scheme 1).

Scheme 1



C−H activation has attracted considerable attention owing to its higher atom economy, shorter synthetic routes, and readily available precursors.[5] Numerous efforts have been devoted to develop the synthesis of oxindoles[6] from amides via C−H activation methods or related C−C bond formation methods.[7] These powerful methods require a specifically functionalized starting material and result in a special

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10.1021/ol101664y
Published on Web 09/14/2010

subclass of oxindoles. To our knowledge, the synthesis of diperoxy oxindole has not been reported yet, and dihydroxy oxindole as a structure motif in nature products such as TMC-95A[8] has never been synthesized effectively from a simple precusor. To complement previous powerful approaches, we now report a new protocol for synthesis of oxindole and dihydroxyindoles based upon C−H activation.

In the initial study, *N*-phenylacrylamide (**1a**) was attempted to react with *tert*-butyl hydroperoxide catalyzed by $Pd(OAc)_2$ in acetic acid without the protection of inert atmosphere. The reaction resulted in diperoxy-oxindole **2a**, and its structure has been identified by single-crystal X-ray diffraction analysis (Figure 1). $Pd(OAc)_2$ was found to be most effective for this

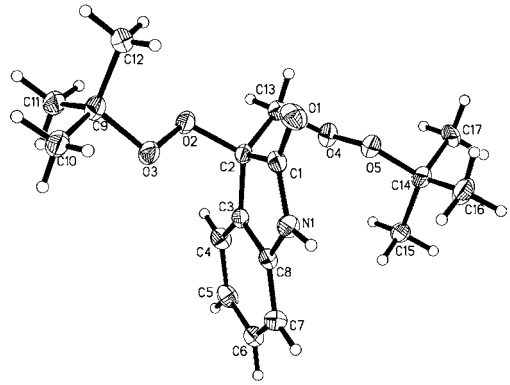

Figure 1. X-ray crystallography for **2a**.

catalytic reaction with the best yield (Table 1, entries 1−5). The variation of catalyst from $Pd(OAc)_2$ to $Pd(PPh_3)_4$ lowered the yield, while $Pd(CH_3CN)_2Cl_2$ and $PdCl_2$ did not promote this reaction at all and starting material was almost recovered in both cases. Additionally, other metal catalysts were tested, and none of them promoted the reaction (see Supporting Information). Meanwhile, the oxidant was found to be crucial for the reactions, and the reaction proceeded smoothly only in the presence of *t*-BuOOH (entries 6−13). Various solvents were tested, and acetic acid was found to be the most efficient media for the reaction (entries 14−17).

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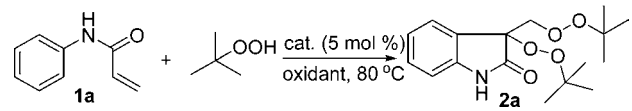
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	oxidant	solvent	yield (%)[b]
1	none	*t*-BuOOH	HOAc	n.r.
2	$Pd(OAc)_2$	*t*-BuOOH	HOAc	70
3	$Pd(PPh_3)_4$	*t*-BuOOH	HOAc	52
4	$Pd(MeCN)_2Cl_2$	*t*-BuOOH	HOAc	n.r.
5	$PdCl_2$	*t*-BuOOH	HOAc	n.r.
6	$Pd(OAc)_2$	$(t\text{-BuO})_2$	HOAc	n.r.
7	$Pd(OAc)_2$	*t*-BuOOAc	HOAc	n.r.
8	$Pd(OAc)_2$	*t*-BuOOBz	HOAc	n.r.
9	$Pd(OAc)_2$	$CuCl_2$,	HOAc	n.r.
10	$Pd(OAc)_2$	$Cu(OAc)_2$	HOAc	n.r.
11	$Pd(OAc)_2$	Ag_2CO_3	HOAc	n.r.
12	$Pd(OAc)_2$	AgOAc	HOAc	n.r.
13	$Pd(OAc)_2$	$PhI(OAc)_2$	HOAc	n.r.
14	$Pd(OAc)_2$	*t*-BuOOH	CF_3COOH	n.r.
15	$Pd(OAc)_2$	*t*-BuOOH	DMSO	n.r.
16	$Pd(OAc)_2$	*t*-BuOOH	DMF	n.r.
17	$Pd(OAc)_2$	*t*-BuOOH	$ClCH_2CH_2Cl$	19

[a] Reaction conditions: 1 mmol of substrate with 10.0 equiv of oxidant and 5 mol % catalyst in 10.0 mL of solvent at 80 °C for 6 h under air. [b] Isolated yields.

With the optimized reaction conditions in hand, the scope and limitation of the reaction were examined with varieties of *N*-arylacrylamide substrates (Figure 2). The diperoxy oxindole products were obtained in moderate to excellent yields. The

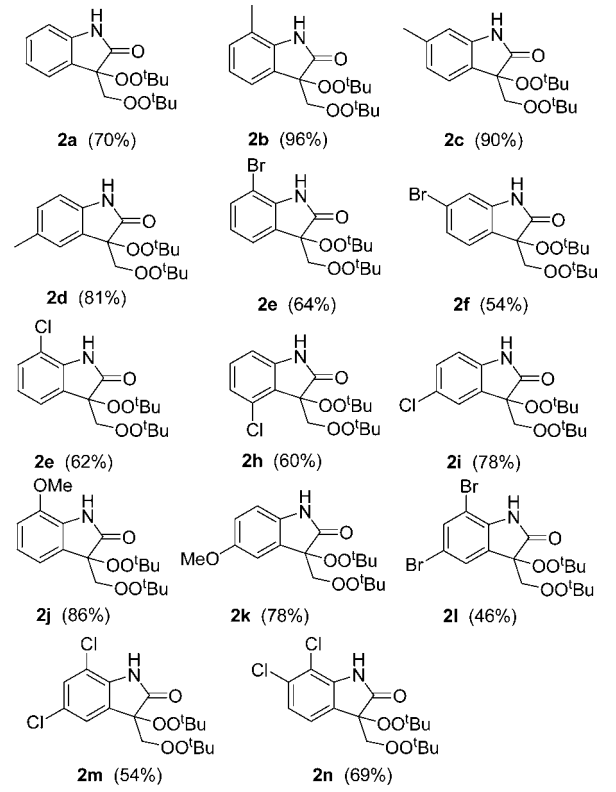
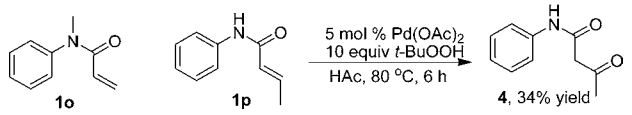


Figure 2. Palladium-catalyzed tandem reaction. (Conditions: **1** (1 mmol) and *t*-BuOOH (10 mmol) in 10.0 mL of acetic acid at 80 °C for 6 h. Isolated yields were reported.)

reaction can tolerate the *ortho*-halo substituents at the aromatic ring and afforded the diperoxidated products with the halogen group remaining (**2e**, **2g**, **2l**, **2m**, and **2n**, Figure 2). The tolerance of *ortho*-halo in the substrates illustrates that this is a new palladium-catalyzed process, which is different from the remarkably powerful Pd-catalyzed intramolecular arylation oxindole synthesis reported by Hartwig[9] and Kundig's radical oxidation formation of oxidoles.[7b,e]

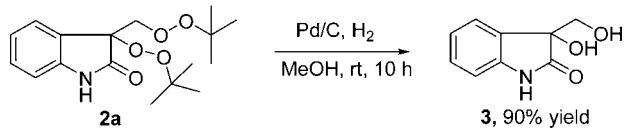
The catalytic system failed for the substrate **1o**, and almost all the starting material was recovered (Scheme 2). Interestingly, for the case of **1p**, no diperoxidated product was found with amide **4** detected in 34% chemical yield (Scheme 2).

Scheme 2



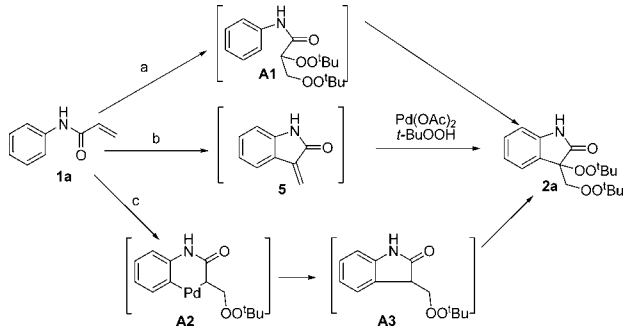
Furthermore, these obtained diperoxy oxindoles can be easily transformed to dihydroxy oxindoles (**3**) by a hydrogenation reaction (Scheme 3). Dihydroxy oxindoles are an important type of biologically active 3-hydroxy oxindoles[10] and can also be transformed into other oxindole analogues.

Scheme 3. Reduction of **2a** to 3-Hydroxy Oxindole Derivative **3**

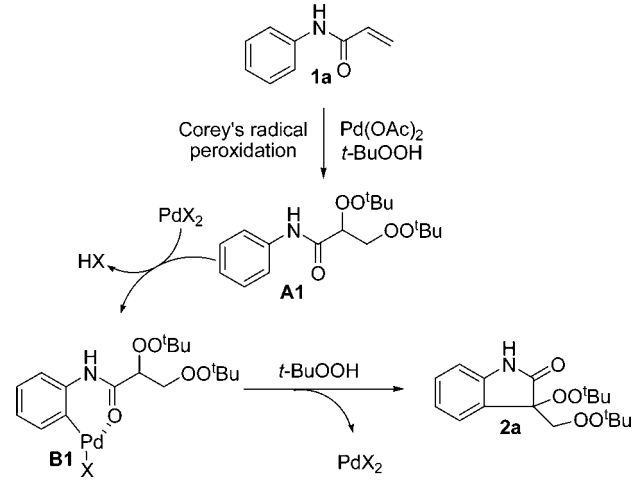


On the basis of the previous studies,[3a,f,4,7a,b,e] we envisioned that *N*-phenylacrylamide may proceed through three proposed tandem pathways to construct a diperoxidated oxindole core structure. The first possible pathway (Scheme 4, pathway a) involves a sequence of diperoxidation and direct couplings of C_{sp2}−H and C_{sp3}−H centers. In the alternative routine (Scheme 4, pathway b), the substrate undergoes aromatic C−H alkenylation (Heck type reaction) followed by diperoxidation. The third possible routine (Scheme 4, pathway c) may proceed through a three-step pathway: a Wacker-type oxidation, reductive elimination, and peroxidation. To investigate the reaction mechanism, attempts to isolate the intermediate **A1** and **A3** were made. However, the cyclization was too rapid, and **A1** and **A3** could not be detected directly in almost all cases. Then, compound **5** was used to examine the possibility of pathway b, but no diperoxy oxindole **2a** was detected under the typical reaction conditions. Attempts to perform the reaction in the presence of radical scavengers (BHT, benzoquinone, or iodine) led only to recovery of **1a**. These inhibitors would not be expected to suppress the Wacker-type oxidation that forms the first step of pathway c.

Scheme 4. Initial Hypothetical Pathway for the Tandem Process



Scheme 5. Proposed Mechanism of the Tandem Process



The proposed mechanism is shown in Scheme 5. First, peroxidation reaction of **1a** occurs, affording diperoxide **A1** through a radical process.[4] Next, **A1** undergoes an electrophilic attacking by cationic Pd(II) on an aromatic C−H bond with the aid of the *ortho* directing group, to generate palladium intermediate **B1**. The ability of the unsubstituted anilide to coordinate Pd(II) while donating electron density into the arene may explain the greater reactivity relative to *N*-alkyl amides. The conversion of the aryl−Pd intermediate to the dihydroindole requires activation of a C−H bond without cleavage of an adjacent peroxide. This is, to our knowledge, an unprecedented transformation. Abstraction of a hydrogen to create a carbon radical appears unlikely given the results with radical inhibitors described above; in addition, an α-peroxyl radical would be expected to rapidly fragment to form a ketone. The presence of Pd(II) and *t*-BuOOH could in theory oxidize the C−H bond to form a reactive cation. However, it is more likely that the aryl−Pd(II) intermediate inserts into the neighboring C−H bond to form

an Ar−Pd−R intermediate which can undergo reductive elimination to establish the C−C bond.

In summary, we have developed a novel and facile palladium-catalyzed tandem process via diperoxidation and C−H activation. This is really the first highly efficient catalytic diperoxidation reaction by using readily available starting materials. The current system provides a new pathway for the synthesis of biologically active diperoxides, as well as oxindole functionalities. The following research will focus on bioactivity investigation of the new series of diperoxy-oxindoles, and the new methodology will be used to access a series of 3-hydrooxindoles of interest for biological investigation.

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Acknowledgment. We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 20772056 and 20932004). The Jiangsu 333 program (for Pan) and the setup fund of Nanjing University (for Han) are also acknowledged.

Supporting Information Available: Experimental procedures, full spectroscopic data for new compounds, and single-crystal X-ray diffraction analysis of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101664Y