

B₂pin₂-Mediated Palladium-Catalyzed Diacetoxylation of Aryl Alkenes with O₂ as Oxygen Source and Sole Oxidant

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S Supporting Information

ABSTRACT: A novel palladium-catalyzed alkene diacetoxylation with dioxygen (O_2) as both the sole oxidant and oxygen source is developed, which was identified by ¹⁸O-isotope labeling studies. Control experiments suggested that bis(pinacolato)diboron (B₂pin₂) played a dominant intermediary role in the formation of a C-O



bond. This method performed good functional group tolerance with moderate to excellent yields, which could be successfully applied to the late-stage modification of natural products. Furthermore, an atmospheric pressure of dioxygen enhances the practicability of the protocol.

xidative transformation is challenging due to its poor selectivity and produces significant quantities of unwanted byproducts derived from the stoichiometric strong oxidants.¹ As a gentle oxidant, molecular oxygen exhibits enormous appeal due to its nature, low cost, and sustainability in transition-metal-catalyzed oxidation reactions, especially in palladium catalysis.² Although there are various examples that the metal catalysts could be directly reoxidized by oxygen, the metal-catalyzed aerobic oxidation fails at times because of the low solubility of oxygen in organic solvent and the slow electron transfer between metal to O_2 in comparison with the decomposition of the low valent metal catalyst.³

Palladium-catalyzed selective aerobic oxidation of olefins into value-added products is one of the most important transformations in modern organic synthesis. One of the major challenges that remains in the selective aerobic oxidation of olefin is to accelerate the regeneration of the Pd^{II} catalyst and suppress the precipitation of palladium black. Since the seminal discovery of palladium/copper-catalyzed aerobic oxidation of olefins (Wacker oxidation),⁴ in which copper salt acts as the electron transfer mediator (ETMs), extensive efforts have been devoted to exploring efficient ETMs as a co-oxidant in recent decades.⁵ For example, Grubbs and Kang independently reported AgNO₂ and ^tBuNO₂ as ETMs to realize selective aldehyde and ketone formation (Scheme 1, eq 1).^{6a,c} This approach has also been utilized in difunctionalization of olefins, in which nitrite was used as ETMs.^{6b,d} A high pressure of oxygen is another strategy to increase the rate of reoxidation of palladium species (Pd0 or Pd-H). Kaneda and co-workers reported the Wacker process with the PdCl₂-DMA system under 6 atm of oxygen.^{7a} The diacetoxylation of olefin under 8 atm of oxygen was demonstrated by our group. $^{7\mathrm{b},\mathrm{c}}$ Herein, we report a B₂pin₂-mediated palladium-catalyzed diacetoxylation of olefin under 1 atm of oxygen, in which the C-O bond is rapidly formed by aerobic oxidative C-B bond cleavage instead of the disfavored palladium-mediated C-O bond reductive elimination.⁸ Meanwhile, the ligand stabilizes the

Scheme 1. Pd-Catalyzed Aerobic Oxidation of Olefins

ETM strategy: (ref 6a-d) R or R OAc (1) Pd(II) catalyst / O2 CuCl₂ or nitrites as ETMs High pressure oxygen (ref 7a-c) Pd(II) catalyst (2) O₂ (high pressure) Ligand assisted rapid C-B bond formation followed by oxygenation OAc Pd(II) catalyst / ¹⁸O₂ (balloon) OAc (3) B₂pin₂ R^1 R^2 R¹ ← R² − Pd/O₂ B₂pin₂

possible Pd-H species and prevents the deactivation of catalyst (Scheme 1, eq 3).

After detailed examinations of different parameters,^{9,10} the best conditions for the diacetoxylation reaction are as follows: Pd(OAc)₂ (7.5 mol %), terpy (10 mol %), B₂pin₂ (1.2 equiv), and AcOH (5 equiv) in CH_3CN/Ac_2O (0.15 M, v/v = 1:1) at 90 °C under an O₂ balloon (see the Supporting Information for details). With the optimized reaction conditions in hand, we sought to explore styrenes containing diverse functional groups. As shown in Scheme 2, substitutions in the para position with both electron-donating and -withdrawing groups (EWGs) were tolerated, and these styrenes transferred to the corresponding products with good to excellent yields (2a-2i). It is noteworthy that the reaction time of substrates with EWGs was longer than those with electron-donating groups (EDGs) for improving the conversion rate. Furthermore, the styrenes with benzyl chloride 2k and alkynyl moieties (2x)

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Scheme 2. Substrate Scope of Terminal Alkenes⁴



^{*a*}Reaction conditions: alkenes 1 (0.3 mmol), Pd(OAc)₂ (7.5 mol %), terpy (10 mol %), B₂pin₂ (1.2 equiv), AcOH (5.0 equiv) in CH₃CN/ Ac₂O (0.15 M, v/v = 1/1) with O₂ balloon at 90 °C. The reaction time depended on different substrates by TLC detection. Isolated yield.

proceeded smoothly under the standard conditions. Additionally, *meta-, ortho-*, and multisubstituted styrenes also exhibited good reactivities to afford the target products 2l-2v in moderate to good yields. When the conjugated diene substrate 2y was employed under the standard conditions, diacetoxylation of the terminal double bond was observed, while the internal double bond was retained, which showed exclusive regioselectivity.¹¹ Notably, sulfur-, nitrogen-, and oxygen-containing heteroaromatic ethenes could be also converted into the desired products with satisfactory yields (2z-2ae).

Next, the scope of aromatic internal alkenes was examined. When β -methylstyrene derivatives were employed in the reaction, the desired products were obtained with antidiastereoselectivity to a certain extent, especially for the electron-deficient double bonds (2af-2ai, Scheme 3). Besides, the Z/E configuration of double bond has a small influence on the diastereoselectivity of products (2af, 2aj), which indicated that the formation of two C-O bonds was a multistep process. The group of triflate, benzyl ether, and alkyl ester could be tolerated under the standard conditions (2ah, 2aj, 2ak). The transformation of (E,E)-1,4-diphenyl-1,3-butadiene gave the desired product 2al with a single double bond reserved in 90% total yield. Inactive double bonds were inert under the current conditions (2am, 2an). Finally, trisubstituted and cyclic internal alkenes showed good reactivity under the standard conditions, despite an extended reaction time. The diaster-

Scheme 3. Substrate Scope of Internal Alkenes^a



^{*a*}Reaction conditions: alkenes 1 (0.3 mmol), Pd(OAc)₂ (7.5 mol %), terpy (10 mol %), B₂pin₂ (1.2 equiv), AcOH (5.0 equiv) in CH₃CN/ Ac₂O (0.15 M, v/v = 1:1) in reaction tube with O₂ balloon at 90 °C. The reaction time depended on different substrates by TLC detection. Isolated yields are reported as a mixture of *syn/anti*products. The ratios of *syn* and *anti* products were determined by ¹H NMR or isolated yields. Unless otherwise noted, double bonds are *E* configuration. ^{*b*}Substrates is *Z* configuration. ^{*c*}Substrates is *E* configuration. ^{*d*}Substrate **1ah** is a *Z/E* (1:5.2) mixture.

eoselectivity was also consistent with the electric nature of olefins (2ao-2ar).

In order to test the applicability and universality of this protocol a complex structural system, the late-stage modification of natural product derivatives was implemented. The styrenes derived from estrone, cholesterol, and glucose were subjected to the optimized conditions (Scheme 4). Gratifyingly, the diacetoxylation reaction proceeded smoothly to afford **2as**, **2at**, and **2au** with 78%, 55%, and 67% yields, respectively. Importantly, excellent diastereoselectivity was observed in these transformations.

Scheme 4. Diversification of Natural Product Derivatives^a



^{*a*}Reaction conditions: alkenes **1** (0.1 mmol), Pd(OAc)₂ (7.5 mol %), terpy (10 mol %), B₂pin₂ (1.2 equiv), AcOH (5.0 equiv) in CH₃CN/ Ac₂O (0.15 M, v/v = 1/1) in reaction tube with O₂ balloon at 90 °C. The reaction time depended on different substrates by TLC detection. Isolated yield. The ratios of dr were determined by ¹H NMR analysis. To gain deep sight into this transformation, some control experiments and isotope labeling studies were conducted. When phenethyl borate 4 was employed under the standard conditions, the acetoxylation product 5 of the borate group was isolated in 92% yield, which had never been reported until now (Scheme 5, eq 4). In the crossover experiment, when



using the mixture of acetic anhydride and propanoic anhydride in place of acetic anhydride, four products 7, 8a, 8b, and 9 were obtained in 25%, 24%, 13%, and 12% yields, respectively, which suggested that two ester groups were installed through independent steps during the reaction (Scheme 5, eq 5). Furthermore, when *meso*-3ai was subjected to the standard conditions, the diacetoxylation product 2ai was obtained with higher yield and similar diastereoselectivity compared with that of 1ai serving as the substrate (Scheme 5, eq 6). This result indicated that the hydroxyl could be acetylized under the standard conditions via the possible carbocation.

A subsequent ¹⁸O-labeling experiment gave the unlabeled diacetoxylation product **2a** (27.2%), mono ¹⁸O-labeled product (61%), and doubly ¹⁸O-labeled product (12%), which were determined by high resolution mass spectrometry (Table 1).^{12a,b} After hydrolysis of the isotopic mixture **2a**, the oxygen-



18 abundance was almost retained, which demonstrated that the ¹⁸O label was incorporated into the $C(sp^3)$ –O bond and the acyl groups were derived from anhydride. More importantly, dioxygen as an oxygen source was involved in the formation of the target product.

Based on the above results and the literature precedents,^{7b,12} a proposed mechanism is shown (Scheme 6I). The reaction was initiated by *trans*-acetoxypalladation with alkene 1 to provide organopalladium intermediate B, which was sequentially transmetalated with B_2pin_2 to form the intermediate C.^{12a,b,13} The intermediate C might promote the H atom transfer from AcOH to palladium, forming [Pd–H] species





D.^{10b,14} Next, O₂ was directly inserted into the palladiumhydride intermediate **D** to afford a palladium hydroperoxide species **E**,^{3e,g} which facilitated the oxidation of the C–B bond of compound **10** similar to the process of hydroboration– oxidation via the transient state **F**.¹⁵ Subsequently, the complex **F** liberated the precursor **11** of the diacetoxylation product and palladium complex **G**, which underwent ligand exchange with AcO⁻ to regenerate the palladium species **A** and H₂O. The hydroxyacetate **11** could be detected by HRMS-ESI in the reaction mixture.

Next, the hydroxyacetate 11 could be quickly transformed into the major single labeled product via direct acetylization by Ac_2O (Scheme 6II, path 1) or S_N1 nucleophilic substitution (path 2), which depended on the steric hindrance and electronic effect from the results of substrate scope. Therefore, the isotope unlabeled products were delivered from nucleophilic substitution of AcO^- , while the double isotope labeled products were derived from the acetoxypalladation and later direct acetylization (path 1) or the acetoxypalladation and later nucleophilic substitution (path 2), with ¹⁸O-labeled AcO^- .

In summary, we have successfully developed a unique palladium-catalyzed diacetoxylation process of alkenes with atmospheric pressure dioxygen as both the oxygen source and sole oxidant, in which B_2pin_2 plays an important intermediary role in the formation of the C–O bond via the oxidative cleavage of the C–B bond. Consequently, a diverse range of functional groups were shown to be compatible with the chemo- and diastereoselective process. The present method also exhibits potential application value in the late-stage modification of natural products. We believe that the strategy of direct activation of dioxygen to realize a variety of difunctionalization of alkene will be available soon.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b01806.

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

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Notes

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