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Palladium-Catalyzed Oxidative Allylic Alkylation of *N*-Hydroxyimides

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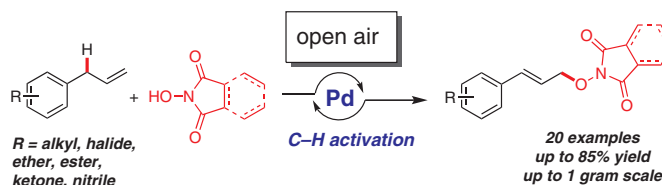Milind M. Ahire
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R = alkyl, halide, ether, ester, ketone, nitrile

open air

Pd

C–H activation

20 examples
up to 85% yield
up to 1 gram scale

Abstract A palladium-catalyzed oxidative C–H allylic alkylation of *N*-hydroxyimides has been developed. This transformation provided valuable *N*-allyloxypyrrolidinediones in moderate to excellent yields using operationally simple, ligand free, and mild reaction conditions. The reaction tolerated broad and variable substituents on allylarenes and *N*-hydroxyimides.
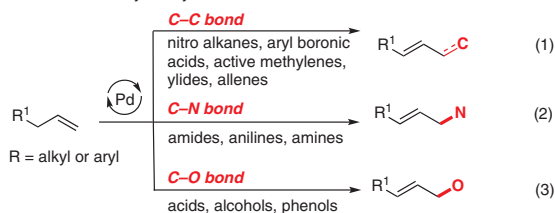
Key words allylic C–H activation, palladium, *N*-hydroxyimides, C–O bond formation

Construction of C_{sp^3}–oxygen, C_{sp^3}–C_{sp^3}, and C_{sp^3}–nitrogen bond can be efficiently achieved using the classic palladium-catalyzed Tsuji–Trost allylic alkylation.[1] The reaction involves a Pd-η^3-π-allyl complex, which undergoes attack by various nucleophiles. The reaction, however, requires allylic substrates to be pre-oxidized. Transition-metal-catalyzed oxidative allylic alkylation is a privileged synthetic transformation, which provides strategic advantages in access of C–C and C–X (carbon–heteroatom) bonds with minimum prefunctionalization.[2] Direct oxidation or functionalization of allylic C_{sp^3}–H bonds was first introduced by the White group in 2004 using sulfoxide-promoted, catalytic Pd(OAc)$_2$/benzoquinone (BQ)/AcOH α-olefin allylic oxidation systems.[3a] This chemo- and regioselective transformation proceeds via a serial ligand catalysis mechanism.[3b] The reaction has now been expanded for the construction of C–C bond (Scheme 1, eq. 1),[4] C–N bond (Scheme 1, eq. 2 and 4),[5] and C–O bond (Scheme 1, eq. 3 and 4)[6] to provide functionalized products.
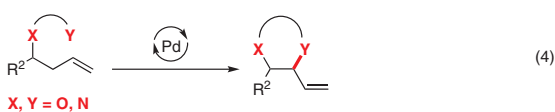
We have sought to extend the scope of oxidative allylic C–H alkylation reaction using oxygen nucleophiles that have heteroatoms directly attached to it. *N*-Hydroxyimides are strategically very important reagents in organic chemis-

Previous work

Intermolecular allylic alkylation

R^1

Pd

C–C bond
nitro alkanes, aryl boronic acids, active methylenes, ylides, allenes

R^1 C (1)

R = alkyl or aryl

C–N bond
amides, anilines, amines

R^1 N (2)

C–O bond
acids, alcohols, phenols

R^1 O (3)

Intramolecular allylic alkylation

R^2 X Y

Pd

X Y
R^2 (4)

X, Y = O, N

This work

Ar H + HO–N

Pd

Ar O–N (5)

**Scheme 1** Palladium-catalyzed allylic alkylation

try. They have been used in peptide synthesis[7] and in radical and electrocatalytic reactions.[8] It was thus envisioned that nucleophiles such as *N*-hydroxysuccinimide (NHS, $pK_a = 6.1$)[9a] and *N*-hydroxyphthalimide (NHPI, $pK_a = 7.0$)[9b] have low basicity to allow their use in allylic substitutions. Such oxygenation of allylic substrates has been reported previously on allylic acetates using NHS and NHPI.[10] Separately benzylic and allylic hydrocarbons have been reported to undergo radical-mediated oxygenation specifically with NHPI.[11] This work expands on the previous reports and presents an alternative method utilizing nonradical process that uses unfunctionalized allylic substrates. The *N*-allyloxypyrrolidinedione products obtained in this reaction can

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serve as convenient synthons for terminal oxygenation[11a] or the installation of the –ONH$_2$ group,[12] which is an important moiety in biologically active molecules. Hydroxylamine derivatives obtained easily from these pyrrolidinediones exhibit important anticancer, antibacterial, and antimalarial activities.[13] Separately, their structural features allow them to be used as excellent directing groups in transition-metal-catalyzed C–H activation reactions[14a] as well as aminating reagents in C–H activation reagents.[14b]

Toward the goal of identifying suitable reaction conditions for the transformation, preliminary evaluation was conducted on commercially available 4-allyl anisole (**1a**) as the allylic substrate (Table 1). A trial reaction with **1a** (0.2 mmol scale) and N-hydroxysuccinimide (NHS, **2a**, 2 equiv) as the nucleophilic partner in the presence of Pd(OAc)$_2$ (0.1 equiv) as the catalyst and benzoquinone (BQ, 2 equiv) as the

oxidant[3a] in 1,4-dioxane did not work (entry 1). A quick survey of solvents using the above conditions proved that acetonitrile was better than 1,4-dioxane and dichloroethane (entries 2–4). To our delight, the desired product **3a** was isolated in 23% yield using acetonitrile as the solvent at 40 °C (entry 4). Increasing the reaction temperature to 75 °C improved the yields to 40% (entry 5). Commercially available White catalyst in the presence of BQ provided a low yield (entry 6). At this point, we wished to screen palladium catalysts and oxidants for the reaction. Four additional oxidants were screened including O$_2$,[15a] PhI(OAc)$_2$,[15b] Cu(OAc)$_2$,[15c] and Cu(OTf)$_2$.[15d] The reaction works with oxygen as the terminal oxidant in 46% yield (entry 7). PhI(OAc)$_2$ was found to be less efficient oxidant providing the desired product in only 29% yield (entry 8). Stoichiometric Cu(OAc)$_2$ and Cu(OTf)$_2$ were both tried with catalytic Pd(OTf)$_2$ for the

Table 1 Optimization of Allylic Functionalization
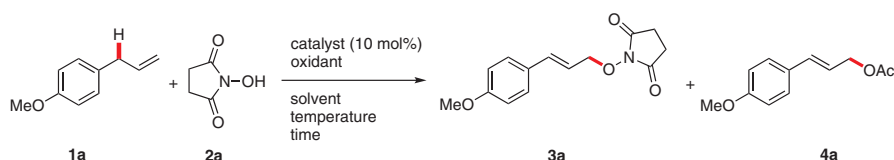
Entry[a]	Catalyst	Oxidant (equiv)	NHS (equiv)	Solvent	Temp (°C)[b]	Yield (%)[c]
1	Pd(OAc)$_2$	BQ (2)	2	1,4-dioxane	40	NR
2	Pd(OAc)$_2$	BQ (2)	2	DMSO/1,4-dioxane (1:1)	40	NR
3	Pd(OAc)$_2$	BQ (2)	2	DCE	40	16
4	Pd(OAc)$_2$	BQ (2)	2	MeCN	40	23
5	Pd(OAc)$_2$	BQ (2)	2	MeCN	75	40
6	White catalyst	BQ (2)	2	MeCN	75	15
7	Pd(OAc)$_2$	O$_2$ (1 atm)	2	MeCN	75	46
8	Pd(OAc)$_2$	PhI(OAc)$_2$ (2)	2	MeCN	75	29
9	Pd(OTf)$_2$	Cu(OAc)$_2$ (1)	2	MeCN	75	50
10	Pd(OTf)$_2$	Cu(OTf)$_2$ (1)	2	MeCN	75	NR
11	Pd(OAc)$_2$	Cu(OAc)$_2$ (1)	2	MeCN	75	62
12	PdCl$_2$	Cu(OAc)$_2$ (1)	2	MeCN	75	NR
13	Pd(OAc)$_2$	Cu(OAc)$_2$ (1)	2	MeCN TEMPO (1 equiv)	75	52
14	–	Cu(OAc)$_2$ (1)	2	MeCN	75	NR
15[d]	Pd(OAc)$_2$	Cu(OAc)$_2$ (1)	3	MeCN without AcOH	75	70
16[d]	Pd(OAc)$_2$	Cu(OAc)$_2$ (1)	3	MeCN AcOH (0.5 equiv)	75	84
17[e]	Pd(OAc)$_2$	Cu(OAc)$_2$ (1)	3	MeCN AcOH (0.5 equiv)	75	27

[a] The reactions were carried out at a concentration of 0.1 M and heated for 24–28 h, **1a** (0.05 mmol, 1 equiv), **2a** (2 equiv), Pd catalyst (10 mol%). Abbreviations: MeCN: acetonitrile; BQ: benzoquinone; DMSO: dimethylsulfoxide; TEMPO: 2,2,6,6-tetramethylpiperidine-1-oxyl radical; DCE: dichloroethane; NR: no reaction observed by TLC.
[b] Temperature refers to inside temperature.
[c] Isolated yield.
[d] Conditions: **1a** (0.05 mmol, 1 equiv), **2a** (3 equiv), Pd(OAc)$_2$ (10 mol%), Cu(OAc)$_2$ (1 equiv), 75 °C.
[e] Reaction under strict anaerobic conditions.

reaction. When Cu(OAc)$_2$ was used as the oxidant, the desired product was isolated in 50% yield (entry 9). No C–H activation product was isolated when Cu(OTf)$_2$ was the oxidant in presence of catalytic Pd(OTf)$_2$ (entry 10). Stoichiometric copper(II) acetate was found to be the best oxidant in the presence of Pd(OAc)$_2$ providing **3a** in 62% yield (entry 11). Amongst the palladium catalysts, the more expensive Pd(OTf)$_2$ provided yields similar to Pd(OAc)$_2$ when Cu(OAc)$_2$ was the oxidant [entry 9 (50%) and entry 11 (62%)]. Catalytic PdCl$_2$ did not work for the reaction (entry 12). Additionally, we conducted a reaction in the presence of TEMPO (1 equiv) to investigate the reaction mechanism. The desired product **3a** was obtained in 52% yield confirming that the reaction does not proceed through radical intermediates (entry 13). Radical trapping products were not observed even when the reaction was repeated with TEMPO (3 equiv); instead an increased product yield (65%) was observed. The result confirmed that TEMPO was serving as a co-oxidant for the reaction entry.[16] The reaction does not occur without palladium catalyst (entry 14). The effect of equivalent ratios of allylbenzene **1a** and NHS **2a** was examined, and we found that the yield of **3a** was significantly improved after the equivalents of NHS (**2a**) were increased to 3.0 (entry 15). Additionally, slight improvement in the yield of **3a** was observed after addition of acetic acid (entry 16).[5d] All reactions were conducted under aerobic conditions, and no special precautions were taken to remove dissolved oxygen from the solvent. When dissolved oxygen was completely removed using freeze-thaw cycles and the reaction was conducted under strict anaerobic conditions, the reaction yield fell to 27% percent (entry 17). It is noteworthy to mention that the Z-isomer was not observed. Finally, the linear E-allylic acetate **4a** (10–12%) was the only byproduct formed and was characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. The source of the acetate nucleophile that results in formation of allylic acetate could be acetic acid, palladium catalyst (Pd(OAc)$_2$), or the oxidant (Cu(OAc)$_2$).

Once the reaction was optimized, a number of allyl benzene substrates (**1a–p**, see Table 1 in Supporting Information), either commercially available or prepared using known protocols from the corresponding aryl bromides, were subjected to the reaction conditions.[17] Scheme 2 provides a summary of the scope of the developed protocol. A
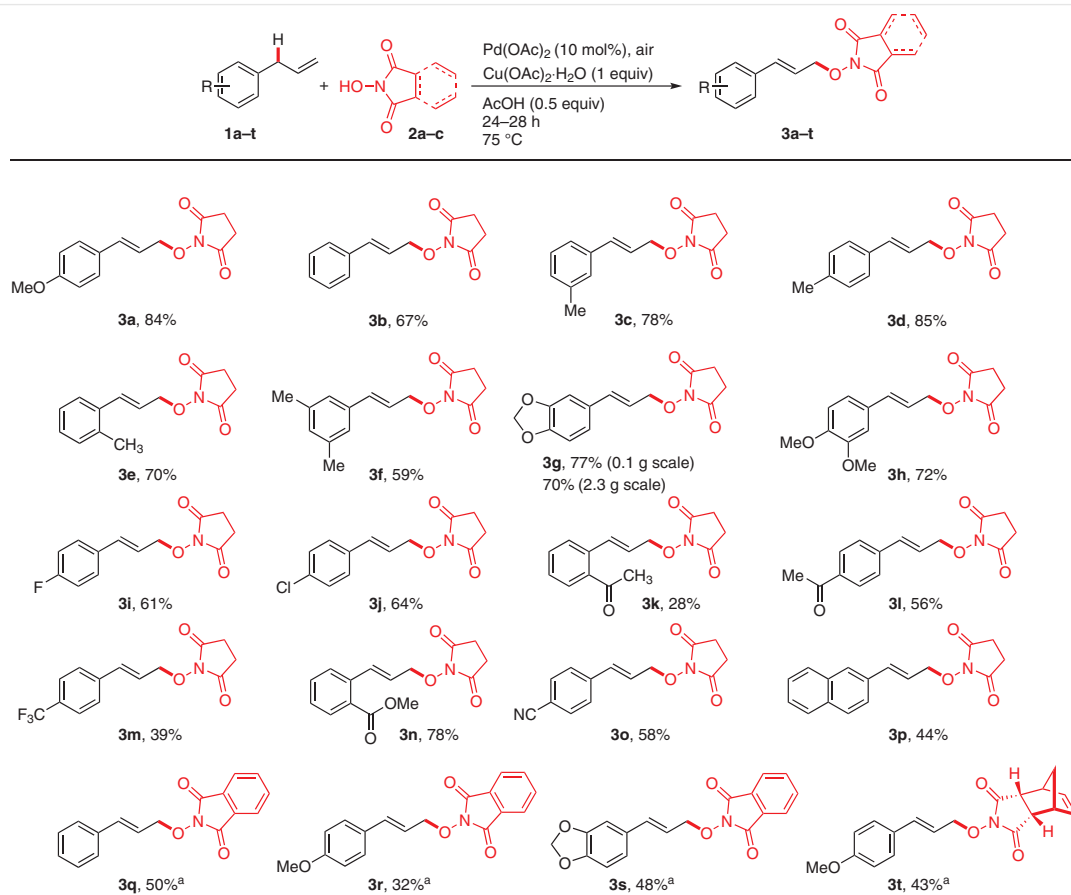
Scheme 2 Substrate scope for allylic C–H activation. *Reagents and conditions:* **1a** (0.05 mmol, 1 equiv), **2a** (3 equiv), Pd(OAc)$_2$ (10 mol%), Cu(OAc)$_2$ (1 equiv), AcOH (0.5 equiv), MeCN (0.1 M), 75 °C. [a] With 20 mol% Pd(OAc)$_2$.

variety of substituents including various electron-donating and electron-withdrawing groups on allylbenzenes were tested, and the corresponding products were obtained in moderate to good yields (Scheme 2). Separately, NHS (**3a–p**), NHPI (**3q–s**), and *N*-hydroxy-5-norbornene-2,3-dicarboxylic acid imide (**3t**) were evaluated as nucleophiles successfully.

In the optimization study, the 4-methoxy-1-allylbenzene (**1a**) reacts with NHS and provided the desired product in 84% yield (Table 1, entry 16). The unsubstituted allylbenzene gave the respective product **3b** in good yield (Scheme 2). The methyl-substituted allylbenzenes were found to be good substrates for this transformation, and the corresponding products **3c–f** were obtained in good yields. In addition, electron-rich allylarenes **1g** and **1h** reacted smoothly, and the expected products **3g** and **3h** were obtained in good chemical yields. The developed reaction conditions also tolerated halides on allylbenzenes and delivered the oxidation products **3i** and **3j** in good yields. Allylbenzenes with electron-withdrawing substituents such as ketone (**1k** and **1l**) at the *ortho* and *para* position of the phenyl ring, trifluoromethane (**1m**), ester (**1n**), and nitrile (**1o**), afforded the alkylation of NHS (**3k–o**) in moderate yields. The 2-allylnaphthalene substrate (**1p**) performed well, furnishing the product **3p** in modest yield. Furthermore, we observed 10–15% of the allylic acetate formation in all of the above substrates. Gratifyingly, the developed protocol gave a 70% yield when tested on gram scale (Scheme 2, 3g).

Two experiments were conducted to investigate the mechanism of the reaction (Scheme 3). To rule out allylic acetate as an intermediate, we performed the reaction using *E*-allylic acetate **4a** under optimized reaction conditions. The linear oxidation product **3a** was not observed under these conditions (Scheme 3, eq. 1). Separately, a cross-oxidation experiment was conducted where both 4-methoxy-allylbenzene (**1a**) and *E*-allylic acetate (**4b**) were used together. Interestingly, only the C–H activation product **3a** was the isolated in 70% yield (Scheme 3, eq. 2). The compound **4b** was recovered and we did not observe the formation of **3b**. This confirmed that the mechanism involves allyl C–H bond activation to afford a π-allyl palladium intermediate which is then attacked by the oxygen nucleophile from *N*-hydroxyimide.

On the basis of control experiments and previous works by the White group, the plausible reaction mechanism is depicted in the Scheme 4. First, Pd(OAc)$_2$ activates the allylic C–H bond of **1** to form η^3-π-allyl palladium complex [**I**]. The electron-deficient complex **I** undergoes a nucleophilic attack with NHS and generates complex **II**. Under the reaction conditions complex **II** breaks to form desired compound **3** and the Pd^0, which is then oxidized by Cu(OAc)$_2$ to regenerate the active Pd(II) catalyst. Since only one equivalent of 1e$^-$ oxidant Cu(II) was used, we believe that dissolved oxygen serves as the terminal oxidant.[18] This transformation constitutes the first example of Pd-catalyzed oxidative allylic C–H bond activation followed by alkylation of *N*-hydroxyimides.
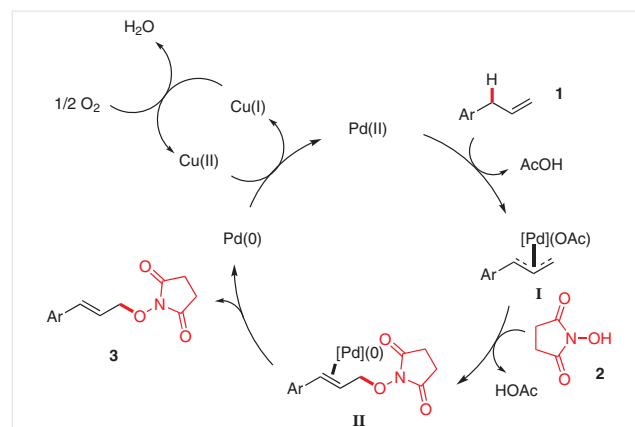
Scheme 4 Proposed catalytic cycle

In conclusion, we have developed novel, mild, and scalable Pd-catalyzed oxidative C–H allylic alkylation of *N*-hydroxyimides.[19] Various substituted allylarenes can be tolerated in this reaction to provide the corresponding linear allyloxypyrrolidinediones with moderate to excellent yields. We are currently investigating the application of this method for the synthesis of a small library of bioactive compounds.
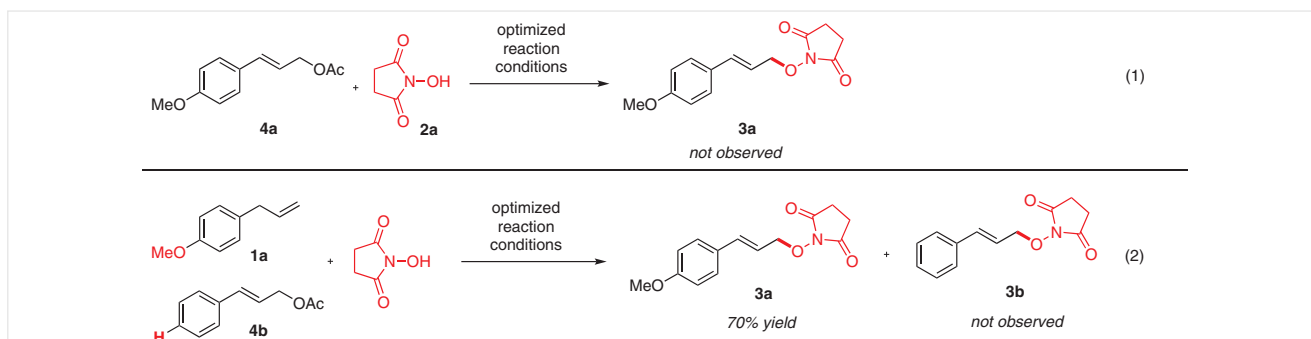
Scheme 3 Control experiments

Letter

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691508.

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(19) **General Procedure for C–H Activation/C–O Bond Formation**
To a solution of aryl benzene **1** (0.1 mmol, 1 equiv) in acetonitrile (2 mL) were added *N*-hydroxyimide (**2**, 3.0 equiv), copper(II) acetate monohydrate (1.0 equiv), acetic acid (0.5 equiv), and Pd(OAc)$_2$ (0.1 equiv) in the same order and heated at 75 °C. The reaction was conducted in a round-bottom flask equipped with a reflux condenser. After 24–28 h, the reaction mass was dried on a small mass of silica and was purified by flash chromatography using hexanes/EtOAc .
(*E*)-1-[(3-(4-Methoxyphenyl)allyl)oxy]pyrrolidine-2,5-dione (3a)
Prepared according to the general procedure. Purification by column chromatography (*n*-hexane/EtOAc, 4:1) gave **3a** in 84% yield as a white solid (mp 98–100 °C). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.34–7.30 (d, *J* = 8.6 Hz, 2 H), 6.87–6.84 (d, *J* = 8.7 Hz, 2 H), 6.60 (d, *J* = 15.9 Hz, 1 H), 6.25–6.18 (dt, *J* = 15.8, 7.3 Hz, 1 H), 4.77 (dd, *J* = 7.3, 1.0 Hz, 2 H), 3.80 (s, 3 H), 2.65 (s, 4 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.5, 160.0, 137.5, 128.4, 128.2, 119.2, 114.1, 77.7, 55.3, 25.4. HRMS: *m/z* calcd for C$_{14}$H$_{16}$NO$_4$ [M + H$^+$]: 261.1001; found: 261.1066.