Palladium-Catalyzed Oxidative Allylic Alkylation of N-Hydroxyimides

Narasimham Ayyagari◊
Sunil Kumar Sunnam◊
Milind M. Ahire
Minxi Yang
Kevin Ngo
Jitendra D. Belani*  0000-0003-4876-0044

Department of Pharmaceutical Sciences, School of Pharmacy, Thomas Jefferson University, 901 Walnut St, Ste. 919, Philadelphia, PA 19107, USA
jitendra.belani@jefferson.edu

◊ The authors contributed equally to the project

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

Scheme 1 Palladium-catalyzed allylic alkylation

Previous work

Intermolecular allylic alkylation

C–C bond

R1

R2

X, Y = O, N

This work

Intramolecular allylic alkylation

R2

X, Y = O, N

Construction of C(sp3)–oxygen, C(sp3)–C(sp3), and C(sp3)–nitrogen bond can be efficiently achieved using the classic palladium-catalyzed Tsuji–Trost allylic alkylation.1 The reaction involves a Pd-η3-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(sp3)–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 chemistry. They have been used in peptide synthesis7 and in radical and electrocatalytic reactions.8 It was thus envisioned that nucleophiles such as N-hydroxysuccinimide (NHS, pKa = 6.1)9a and N-hydroxyphthalimide (NHPI, pKa = 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
serve as convenient synthons for terminal oxygenation\textsuperscript{11a} or the installation of the $–\text{ONH}_2$ group,\textsuperscript{12} which is an important moiety in biologically active molecules. Hydroxylamine derivatives obtained easily from these pyrrolidinediones exhibit important anticancer, antibacterial, and antimalarial activities.\textsuperscript{13} Separately, their structural features allow them to be used as excellent directing groups in transition-metal-catalyzed C–H activation reactions\textsuperscript{14a} as well as amating reagents in C–H activation reagents.\textsuperscript{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\textsuperscript{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$_2$,\textsuperscript{15a} Phl(OAc)$_2$,\textsuperscript{15b} Cu(OAc)$_2$\textsuperscript{15c} and Cu(OTf)$_2$.\textsuperscript{15d} The reaction works with oxygen as the terminal oxidant in 46% yield (entry 7). Phl(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 oxidant\textsuperscript{13a} 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$_2$,\textsuperscript{15a} Phl(OAc)$_2$,\textsuperscript{15b} Cu(OAc)$_2$\textsuperscript{15c} and Cu(OTf)$_2$.\textsuperscript{15d} The reaction works with oxygen as the terminal oxidant in 46% yield (entry 7). Phl(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

<table>
<thead>
<tr>
<th>Entry$^a$</th>
<th>Catalyst</th>
<th>Oxidant (equiv)</th>
<th>NHS (equiv)</th>
<th>Solvent</th>
<th>Temp (°C)$^b$</th>
<th>Yield (%)$^c$</th>
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<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>BQ (2)</td>
<td>2</td>
<td>1,4-dioxane</td>
<td>40</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>BQ (2)</td>
<td>2</td>
<td>DMSO/1,4-dioxane (1:1)</td>
<td>40</td>
<td>NR</td>
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<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>BQ (2)</td>
<td>2</td>
<td>DCE</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>BQ (2)</td>
<td>2</td>
<td>MeCN</td>
<td>40</td>
<td>23</td>
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<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>BQ (2)</td>
<td>2</td>
<td>MeCN</td>
<td>75</td>
<td>40</td>
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<td>6</td>
<td>White catalyst</td>
<td>BQ (2)</td>
<td>2</td>
<td>MeCN</td>
<td>75</td>
<td>15</td>
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<td>7</td>
<td>Pd(OAc)$_2$</td>
<td>O$_2$ (1 atm)</td>
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<td>MeCN</td>
<td>75</td>
<td>46</td>
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<tr>
<td>8</td>
<td>Pd(OAc)$_2$</td>
<td>Phl(OAc)$_2$ (2)</td>
<td>2</td>
<td>MeCN</td>
<td>75</td>
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<td>9</td>
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<td>MeCN</td>
<td>75</td>
<td>50</td>
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<td>Cu(OTf)$_2$ (1)</td>
<td>2</td>
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<td>75</td>
<td>NR</td>
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<td>Pd(OAc)$_2$</td>
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<td>MeCN</td>
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<td>12</td>
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<td>75</td>
<td>NR</td>
</tr>
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<td>13</td>
<td>Pd(OAc)$_2$</td>
<td>Cu(OAc)$_2$ (1)</td>
<td>2</td>
<td>MeCN/TEMPO (1 equiv)</td>
<td>75</td>
<td>52</td>
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<tr>
<td>14</td>
<td>–</td>
<td>Cu(OAc)$_2$ (1)</td>
<td>2</td>
<td>MeCN</td>
<td>75</td>
<td>NR</td>
</tr>
<tr>
<td>15$^d$</td>
<td>Pd(OAc)$_2$</td>
<td>Cu(OAc)$_2$ (1)</td>
<td>3</td>
<td>MeCN/without AcOH</td>
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<td>70</td>
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<tr>
<td>16$^d$</td>
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<td>Cu(OAc)$_2$ (1)</td>
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<td>MeCN/ AcOH (0.5 equiv)</td>
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<td>84</td>
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<tr>
<td>17$^e$</td>
<td>Pd(OAc)$_2$</td>
<td>Cu(OAc)$_2$ (1)</td>
<td>3</td>
<td>MeCN/ AcOH (0.5 equiv)</td>
<td>75</td>
<td>27</td>
</tr>
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</table>

$^a$ 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 \[\text{(entry 9 (50%) and entry 11 (62%)}.\right.\] 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. 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). 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. 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. *With 20 mol% Pd(OAc)$_2$. © 2020. Thieme. All rights reserved. Synlett 2020, 31, 87–91
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 3, 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 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 π3-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 Pd⁰, 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. This transformation constitutes the first example of Pd-catalyzed oxidative allylic C–H bond activation followed by alkylation of N-hydroxyimides.

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

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

References and Notes

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