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Palladium(II)-Catalyzed Direct Conversion of Allyl Arenes into Alkenyl Nitriles

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A mild palladium-catalyzed ammoxidation approach, which leads to the formation of \( \equiv \text{C}=\text{N} \) triple bond from allyl group, has been developed to directly convert allylarenes into alkenyl nitriles.

**Introduction**

Alkenyl nitriles are both unique structural units in organic synthesis and versatile building blocks of natural products, agricultural chemicals, pharmaceuticals, and dyes.1 Due to their important applications in various fields, efforts have been devoted to the development of efficient synthetic methods for this type of nitrile compounds.2 However, most of the methods so far developed are based on functional group transformations or addition reactions. To the best of our knowledge, there is only one case in which a Fe-catalyzed direct conversion of the allyl bond transformation of allyl arenes into the corresponding unsaturated nitriles has been reported.3,4 Qin and Jiao has demonstrated the oxidative C-H functionalization of terminal alkenes, which has emerged as a powerful strategy in organic synthesis.5-9 On the other hand, we have recently reported a direct synthesis of aromatic nitriles from the methyl arenes with Pd(OAc) 2 and tert-butyl nitrite as both the nitrogen source and the oxidant. The reaction proceeds under mild conditions, and the oxidant. The reaction proceeds under mild conditions, and the oxidant. The reaction proceeds under mild conditions, and the oxidant. The reaction proceeds under mild conditions, and the oxidant.

**Results and Discussion**

**Table 1. Optimization of Reaction Conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol%)</th>
<th>TBN (equiv)</th>
<th>Additive (mol%)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Pd(OAc) 2 (10)</td>
<td>3</td>
<td>None</td>
<td>DCE</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc) 2 (10)</td>
<td>3</td>
<td>None</td>
<td>THF</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc) 2 (10)</td>
<td>3</td>
<td>None</td>
<td>Dioxane</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc) 2 (10)</td>
<td>3</td>
<td>None</td>
<td>MeCN</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc) 2 (5)</td>
<td>3</td>
<td>NHPI (30)</td>
<td>MeCN</td>
<td>62</td>
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<tr>
<td>6</td>
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<td>2</td>
<td>NHPI (30)</td>
<td>MeCN</td>
<td>80</td>
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<tr>
<td>7</td>
<td>Pd(OAc) 2 (10)</td>
<td>2</td>
<td>THICA (10)</td>
<td>MeCN</td>
<td>56</td>
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<tr>
<td>8</td>
<td>Pd(OAc) 2 (10)</td>
<td>2</td>
<td>TEMPO (30)</td>
<td>MeCN</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
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<td>2</td>
<td>NHPI (20)</td>
<td>MeCN</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>Cu(II) (10)</td>
<td>2</td>
<td>NHPI (20)</td>
<td>MeCN</td>
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<tr>
<td>11</td>
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<td>NHPI (20)</td>
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</tr>
<tr>
<td>12</td>
<td>Fe(OAc) 2 (10)</td>
<td>2</td>
<td>NHPI (20)</td>
<td>MeCN</td>
<td>trace</td>
</tr>
</tbody>
</table>

**Scheme 1** Pd(OAc) 2-catalyzed cyanation of methyl arenes and allyl arenes.
Similar to our previous study,10 the investigation began with evaluation of the direct transformation of 1-allylbenzene 1a into the corresponding cinnamonitrile 2a under oxidative conditions (Table 1). In the absence of additive, the reaction of 1a catalyzed by 10 mol% of Pd(OAc)2 with tert-butyl nitrite at 60 °C in DCE or THF gave only trace amount of 2a (entries 1 and 2), whereas the reaction in 1,4-dioxane and acetonitrile produced 2a in 14% and 26% yield, respectively (entries 3 and 4). Gratifyingly, 2a was formed in 62% yield in the presence of N-hydroxyphthalimide (NHPI) as an additive in catalytic amount (30 mol%) with 5 mol% of Pd(OAc)2 (entry 5). The reaction could be optimized by using 10 mol% of Pd(OAc)2 at 50 °C (entry 6). We also examined another carbon radical producing catalyst N, N', N'-trihydroxyisocyanuric acid (THICA) as the additive.12 The reaction afforded 2a, albeit in diminished yield. 2,2,6,6-Tetramethyl-1-piperidinyl (TEMPO) has also been examined as additive, however, the reaction only gives 2a in 26% yield (entry 8). Other metal catalysts, including PdCl2(MeCN)2, Cu(OAc)2, CuCl and Fe(OAc)2, have also been examined but they only afford very low yield or trace amount of the product 2a (entries 9-12).

With the optimized reaction conditions, various allylarenes were investigated with 10 mol% Pd(OAc)2 and 30 mol% NHPI as co-catalysts' system (Scheme 2). Electron-donating substituents, such as Me and OMe, at the para, meta, and ortho positions of the arene group did not affect the reaction, affording the corresponding alkenyl nitriles in 67-83% yields (2b-h, 2o). Remarkably, some sensitive substituents or functional groups, such as trimethylsilyl (TMS), Cl and Br, were tolerated well in this transformation (2h, 2i, 2m). Substrates substituted with electron-withdrawing groups, such as F and CF3, also worked well and afforded the desired products in moderate yields (2k, 2n).

It is noteworthy that this reaction also worked with heteroaryl-substituted propene, 1-allyl-2-thiophene (1p), giving 2p in 77% yield. In addition, poly cyclic aromatic-substituted propenes were also successfully converted into corresponding alkenyl nitriles in good yields (2q-s).

Similar to the transformation of methyl arenes into aromatic nitriles,10 a plausible mechanism is proposed as shown in Scheme 3. Initially, as oxidant, tert-butyl nitrite reacts with NHPI to generate the active phthalimide N-oxyl radical (PINO). The tert-butyl nitrite itself decomposes into an NO radical and 2-methyl-...
2-propanol. Then, allyl arene 1 undergoes single-electron-transfer (SET) oxidation with PINO to produce the corresponding allyl radical A. Subsequently, radical recombination of NO radical with A to form intermediate B. Upon isomerization of B to aldoxime C, Pd(OAc)₂-catalyzed dehydration of C finally leads to the desired nitrile product 2. To substantiate this mechanistic hypothesis, we have carried out the reaction of 1a under the standard conditions but in the absence of Pd(OAc)₂ catalyst. The reaction gave a complex mixture, from which oxime C along with the corresponding cinnamaldehyde can be identified by GC-MS.

In conclusion, we have developed a novel Pd(II)-catalyzed direct synthesis of alkenyl nitriles from the corresponding allyl arenes under mild conditions using tert-butyl nitrite as the nitrogen source and inexpensive NHPI as the co-catalyst. Notably, in this transformation, three C=H bonds are cleaved to form one C≡N bond. This reaction offers a novel method for the synthesis of biologically and medicinally important alkenyl nitriles.

Experimental Section

General. All the palladium-catalyzed reactions were performed under nitrogen atmosphere in a flame-dried reaction flask. All solvents were distilled under nitrogen atmosphere prior to use. 1,4-Dioxane and THF were dried over Na with benzophenone-ketyl intermediate as indicator. Acetonitrile and 1,2-dichloroethane were dried over CaH₂. For chromatography, 200-250 mesh silica gel (Qingdao, China) was employed. 1H and 13C NMR spectra were recorded at 400 MHz and 100 MHz with CDCl₃ as the solvent. HRMS were obtained on a Bruker Apex IV FTMS spectrometer. IR spectra were obtained on an Agilent 5975C inert 350 EI mass spectrometer. All reactions were carried out in dry sealed tubes under an atmosphere of nitrogen.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. The starting materials 1a-o and 1q-s were prepared from the corresponding aryl bromide according to a previously reported literature.

The general procedure for Pd(II)-catalyzed reaction.

Carbonyl 2b was used as a starting material for the preparation of oxime 2c as white solid (30 mg, 70% yield).

4. H NMR (CDCl₃, 400 MHz) δ 7.66 (d, J = 8.8 Hz, 2H), 7.38-7.44 (m, 5H), 5.83 (d, J = 16.4 Hz, 1H), 1.33 (s, 9H); 13C NMR (CDCl₃, 100 MHz) δ 154.9, 150.4, 150.0, 127.2, 127.1, 118.4, 95.2, 35.0, 31.1.

trans-2-Methylcinnamonnitrite (2c). The general procedure gave pure 2c as light yellow oil (34 mg, 79% yield). H NMR (CDCl₃, 400 MHz) δ 7.69 (d, J = 16.8 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.30-7.34 (m, 1H), 7.21-7.26 (m, 2H), 5.80 (d, J = 16.8 Hz, 1H), 2.40 (s, 3H); 13C NMR (CDCl₃, 100 MHz) δ 148.4, 137.2, 132.5, 131.0, 130.9, 126.5, 125.5, 118.3, 97.1, 19.5.

trans-2-Methoxylcinnamonnitrite (2f). The general procedure gave pure 2f as light yellow oil (32 mg, 74% yield). H NMR (CDCl₃, 400 MHz) δ 7.37 (d, J = 16.4 Hz, 1H), 7.24-7.32 (m, 4H), 5.86 (d, J = 16.8 Hz, 1H), 2.38 (s, 3H); 13C NMR (CDCl₃, 100 MHz) δ 150.7, 138.9, 133.5, 132.0, 129.0, 127.9, 124.5, 118.2, 96.0, 21.2.

trans-2-Butylcinnamonnitrite (2h). The general procedure gave pure 2h as yellow oil (31 mg, 76% yield). H NMR (CDCl₃, 400 MHz) δ 7.63 (d, J = 16.8 Hz, 1H), 7.37-7.41 (m, 2H), 6.92-6.99 (m, 2H), 6.06 (d, J = 16.8 Hz, 1H), 3.90 (s, 3H); 13C NMR (CDCl₃, 100 MHz) δ 158.3, 146.5, 132.3, 128.9, 122.6, 120.8, 119.0, 111.3, 97.0, 55.6.

trans-4-Methoxylcinnamonnitrite (2j). The general procedure gave pure 2j as white solid (33 mg, 74% yield). H NMR (CDCl₃, 400 MHz) δ 7.39 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 16.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 5.71 (d, J = 16.4 Hz, 1H), 3.84 (s, 3H); 13C NMR (CDCl₃, 100 MHz) δ 162.0, 150.0, 129.0, 126.3, 118.7, 114.5, 93.3, 55.4.

trans-3-Methylcinnamonnitrite (2k). The general procedure gave pure 2k as white solid (33 mg, 74% yield). H NMR (CDCl₃, 400 MHz) δ 7.63-7.66 (m, 2H), 7.04 (d, J = 7.6 Hz, 1H), 6.95-6.99 (m, 2H), 3.83 (s, 3H), 5.86 (d, J = 16.8 Hz, 1H); 13C NMR (CDCl₃, 100 MHz) δ 160.0, 150.4, 134.8, 130.1, 119.9, 118.0, 116.8, 112.4, 96.6, 53.3; IR (neat): ν (M+H) /% 159.1 (M+, 100); HRMS m/z (ESI) calcd for C₁₀H₁₀NO (M+H)⁺: 160.0757, found 160.0752.

trans-4-(Trimethylsilyl)cinnamonnitrite (2l). The general procedure gave pure 2l as yellow oil (41 mg, 73% yield). H NMR (CDCl₃, 400 MHz) δ 7.36-7.44 (m, 5H), 5.83 (d, J = 16.4 Hz, 1H), 1.33 (s, 9H); 13C NMR (CDCl₃, 100 MHz) δ 154.9, 150.4, 127.2, 127.1, 118.4, 95.2, 35.0, 31.1.

trans-4-(Trimethylsilyl)cinnamonnitrite (2l). The general procedure gave pure 2l as yellow oil (46 mg, 76% yield). H NMR (CDCl₃, 400 MHz) δ 7.59-7.63 (m, 2H), 7.38-7.43 (m, 3H), 5.90 (d, J = 16.8 Hz, 1H), 0.28 (s, 9H); 13C NMR (CDCl₃, 100 MHz) δ 150.6, 145.1, 134.0, 133.7, 126.4, 118.2, 96.4, -1.34; IR (neat): ν = 2958, 2218, 1619, 1398, 1249, 1106, 969, 858, 838, 800, 683 cm⁻¹; EI-MS: m/z (%) 205.1 (M⁺, 100); HRMS m/z (ESI) calcd for C₁₀H₁₆NSi (M+H)⁺: 202.1047, found 202.1045.
trans-4-Chlorocinnamonicitrile (2l). The general procedure gave pure 2l as light yellow solid (39 mg, 80% yield).14 H NMR (CDCl3, 400 MHz) δ 7.33-7.39 (m, 5H), 5.8 (d, J = 16.8 Hz, 1H); 13C NMR (CDCl3, 100 MHz) δ 149.1, 137.3, 132.0, 129.4, 128.5, 117.8, 97.0.

trans-4-Bromocinnamicitrile (2m). The general procedure gave pure 2m as yellow solid (49 mg, 78% yield).18 H NMR (CDCl3, 400 MHz) δ 7.55 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 16.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 5.88 (d, J = 16.8 Hz, 1H); 13C NMR (CDCl3, 100 MHz) δ 149.2, 132.4, 128.7, 125.6, 117.8, 97.1.

trans-4-(Trifluoromethyl)cinnamicitrile (2n). The general procedure gave pure 2n as white solid (46 mg, 77% yield).3 H NMR (CDCl3, 400 MHz) δ 7.68 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 16.8 Hz, 1H), 5.99 (d, J = 16.8 Hz, 1H); 13C NMR (CDCl3, 100 MHz) δ 148.8, 136.7, 132.7 (q, J = 32.6 Hz), 127.6, 126.1 (q, J = 3.8 Hz), 123.6 (q, J = 27.0 Hz), 117.3, 99.2.

trans-3,5-(Dimethyl)cinnamicitrile (2o). The general procedure gave pure 2o as white solid (39 mg, 83% yield).15 H NMR (CDCl3, 400 MHz) δ 7.53 (d, J = 16.4 Hz, 1H), 7.05-7.07 (m, 3H), 5.84 (d, J = 16.8 Hz, 1H), 2.33 (s, 3H).13C NMR (CDCl3, 100 MHz) δ 150.9, 138.7, 133.4, 133.0, 125.2, 118.3, 95.7, 21.1; IR (neat): ν = 3019, 2921, 2916, 2330, 2217, 1619, 1601, 1432, 1302, 1166, 1038, 967, 855, 815 cm⁻¹; EI-MS: m/z (%) 151.1 (M⁺, 100); HRMS m/z (ESI) calcld for C9H11N (M⁺) 158.0964, found 158.0960.

trans-3-(Thiophen-2-yl)acrylonitrile (2p). The general procedure gave pure 2p as yellow oil (31 mg, 77% yield).4 H NMR (CDCl3, 400 MHz) δ 7.47 (d, J = 16.4 Hz, 1H), 7.42 (d, J = 5.2 Hz, 1H), 7.24-7.26 (m, 1H), 7.07-7.09 (dd, J = 5.2, 3.6 Hz, 1H), 5.65 (d, J = 16.4 Hz, 1H); 1H NMR (CDCl3, 100 MHz) δ 142.7, 138.4, 131.2, 129.2, 128.3, 118.0, 94.4.

trans-3-(Naphthalen-2-yl)acrylonitrile (2q). The general procedure gave pure 2q as white solid (48 mg, 89% yield).4 H NMR (CDCl3, 400 MHz) δ 7.83-7.87 (m, 4H), 7.52-7.56 (m, 4H), 5.97 (d, J = 16.8 Hz, 1H); 13C NMR (CDCl3, 100 MHz) δ 150.5, 134.5, 133.1, 131.0, 129.6, 129.0, 128.7, 127.8, 127.1, 122.2, 118.3, 96.3.

trans-3-(Naphthalen-1-yl)acrylonitrile (2r). The general procedure gave pure 2r as white solid (46 mg, 86% yield).19 H NMR (CDCl3, 400 MHz) δ 8.24 (d, J = 16.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.88-7.96 (m, 2H), 7.48-7.68 (m, 4H), 5.98 (d, J = 16.4 Hz, 1H); 13C NMR (CDCl3, 100 MHz) δ 147.9, 133.6, 131.5, 130.9, 130.7, 128.9, 127.4, 126.6, 125.4, 124.7, 122.8, 118.2, 98.8.

trans-3-(Phenanthren-9-yl)acrylonitrile (2s). The general procedure gave pure 2s as white solid (50 mg, 80% yield).20 H NMR (CDCl3, 400 MHz) δ 8.62-8.71 (m, 2H), 8.15 (d, J = 16.4 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.82-7.88 (m, 7H), 7.60-7.72 (m, 4H), 5.99 (d, J = 16.4 Hz, 1H); 13C NMR (CDCl3, 100 MHz) δ 148.6, 131.2, 130.7, 130.4, 130.0, 129.3, 129.1, 128.2, 127.3, 127.2, 126.5, 123.8, 123.3, 122.6, 118.0, 99.3; IR (neat): ν = 2924, 2215, 1605, 1494, 1450, 1245, 1148, 959, 820, 750, 722, 669, 656 cm⁻¹; EI-MS: m/z (%) 229.1 (M⁺, 100); HRMS m/z (ESI) calcld for C19H12N2 (M⁺) 230.0964, found 230.0960.

Notes and references

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