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Aerobic Direct C-H Arylation of Nonbiased Olefins

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Supporting Information Placeholder

ABSTRACT: An efficient ligand-promoted biomimetic aerobic oxidative dehydrogenative cross coupling between arenes and nonbiased olefins is presented. Acridine as a ligand was found to significantly enhance the rate, the yield, and the scope of the reaction under ambient oxygen pressure, providing a variety of alkenylarenes via an environmentally friendly procedure.

Direct functionalization of C-H bonds has emerged as a promising tool to create new C-C bonds, and one of the ideal ways is the oxidation of two simple C-H bonds. Among these catalytic dehydrogenative cross-couplings, the “dehydrogenative Heck reaction”, was originally disclosed by Fujiwara and Moritani. Much progress has been achieved in this field following this pioneering work, and this transformation is now fully recognized as a powerful method for the construction of valuable scaffolds. However, recent developments of this reaction have witnessed several restrictions in the presence of simple arenes. Limitations of these approaches include the requirement of a relatively high palladium loading and the use of various inorganic salts as terminal oxidants that provide stoichiometric amounts of reduced external oxidants as waste. In addition, due to their low reactivity, arenes are usually used in a large excess or even as the solvent, thus making the process less attractive in terms of atom economy. The scope of alkenes is also largely limited to “activated” coupling partners such as acrylates and styrene derivatives. On the contrary, electronically nonbiased olefins are not reactive enough to promote the Pd-catalyzed dehydrogenative reaction. Finally, the control of the selectivity is problematic: a mixture of products can be obtained from the insertion of the alkene into the Pd-Ar bond (internal vs external) and the β-hydride elimination (β-H vs β-Ha) (Scheme 1). Consequently a general and efficient protocol solving several of these problems would be desirable.

Based on these considerations, we have explored the aerobic direct C-H functionalization of simple arenes using nonbiased olefins. There are several challenges to deal with during the development of this reaction, the two most critical being the use of an environmentally friendly method and the capacity to engage these much less reactive alkenes efficiently in the coupling. Our laboratory is indeed involved in the development of new sustainable transformations for the creation of C-C bonds via a biomimetic approach.

We evaluated the feasibility of the proposed strategy in the reaction of alkene 1a (1 equiv) with 1,4-dimethoxybenzene 2a (6 equiv) using Pd(OAc)2 (2.5 mol %), p-benzoquinone (BQ) (10 mol %) and iron phthalocyanine [Fe(Pc), 2.5 mol %] in a mixture of acetic acid:dioxane (1:1, v:v) for 24 hours at 90 °C under ambient oxygen pressure (Scheme 2). In this reaction BQ and Fe(Pc) serve as electron-transfer mediators. These reaction conditions provided the desired product 3aa in low yield. As noted above, this unactivated alkene exhibited poor reactivity, and the protocol was further optimized by examining the effect of pyridine (L1) as a ligand. The reaction was very dependent on the palladium/pyridine ratio, and it was found that a 1:1 ratio is optimal. Lower yields were observed with different ratios, and a 20:1 ratio in favor of pyridine (50
mol %) totally inhibited the reaction. A number of both electronically and sterically different pyridine type-ligands (L1-L11) were tested in combination with this catalytic system. Systematic variation of the pyridine moiety revealed that acridine (L3) provided the highest yield. It is interesting to note that no correlation between either the electronic nature or the steric encumbrance of the ligand was observed. Importantly, 3aa was isolated with high levels of selectivity (E2: 18:1, L:B > 1:99).

Scheme 2. Ligand Screening

![Scheme 2](image)

Table 1. Effect of Ligand on Site Selectivity

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>selectivity (α:β)</th>
<th>yield (%)</th>
<th>selectivity (α:β)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>&gt; 5:95</td>
<td>14</td>
<td>46:54</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>L1</td>
<td>19:81</td>
<td>19</td>
<td>47:53</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>&gt; 1:99</td>
<td>53 (49)²</td>
<td>44:56</td>
<td>82 (56)²</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>25:75</td>
<td>23</td>
<td>53:47</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>29:71</td>
<td>25</td>
<td>56:44</td>
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</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>30:70</td>
<td>23</td>
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<td>73</td>
</tr>
<tr>
<td>7</td>
<td>L11</td>
<td>21:79</td>
<td>36</td>
<td>57:43</td>
<td>37</td>
</tr>
</tbody>
</table>

*For reaction conditions, see Scheme 1. ²Isolated yield. ³Ratio of regiosomers determined by NMR spectroscopy of crude mixture. ⁴NMR yield using an internal standard. ⁵Isolated yield.

Scheme 3. Substrate Scope of Alkenes

![Scheme 3](image)

For reaction conditions, see Scheme 1. ²Isolated yield. ³Ratio of isomers (styrenylic) determined by NMR spectroscopy of isolated product. ⁴2a (10 equiv).
**Scheme 4. Substrate Scope of Arenes**

For reaction conditions, see Scheme 1. Isolated yield. Ratio of isomers (α:m:p or α:β) determined by NMR spectroscopy of isolated product. Pd(OAc)\(_2\) (2.5 mol %), L3 (2.5 mol %). Pd(OAc)\(_2\) (1 mol %), L3 (1 mol %). Arene 2 (10 equiv.), Pd(OAc)\(_2\) (5 mol %), L3 (5 mol %). Pd(OAc)\(_2\) (5 mol %), L3 (5 mol %). Reaction performed at 70 °C. Pd(OAc)\(_2\) (3.5 mol %), L3 (3.5 mol %).

The use of purely aliphatic olefins such as 1-octene or 1-undecene gave low yields and poor selectivity.

Alkenes 1a and 1h were selected as model substrates for the arene scope evaluation as presented in Scheme 4.11 Electron-rich arenes undergo smooth coupling with moderate to complete site selectivity in the presence of unsymmetrical substrates (3aa-3ag). Importantly, 3ab could be a relevant synthetic intermediate for the short total synthesis of bioactive compounds abamine and abamine SG.13 Starting from electron-neutral or -poor arenes, a slight increase of the catalyst/ligand loading as well as the amount of arene were necessary for obtaining synthetically useful yields (3ah-3am and 3hn). Additionally, several alkenylated multi-fluoroarenes were also efficiently isolated (3ao-3aq), which is not so frequent for the direct olefination of this category of arenes.12 Because of their high sensitivity to acidic conditions, heterocycles such as thiophenes and furans are usually poor substrates in the oxidative Heck reactions.11 In the present method, these heterocycles efficiently react with unbiased alkenes (3ar-3au and 3hu), leading the desired alkenylated scaffolds in good to high yields at 70 °C.

To obtain mechanistic information, two parallel reactions using 2i and 2i-2l with protected allylamine 1a were performed.16 The comparison of the initial rates gave a kinetic isotope effect of 4.4, indicating that the aromatic C-H bond cleavage by Pd is involved in the rate determining step of the coupling.

**Scheme 5. Acridine Accelerated Reaction**

To gauge the acridine effect, we measured the relative rate of the reaction starting from 1a and 1h with or without ligand (Scheme 5).16 The initial rate of the coupling was roughly 3.6 and 5.4 times faster for 1a and 1h, respectively, in the presence of acridine when compared to the rate in the absence of acridine. In addition, two competitive reactions between 1a and...
REFERENCES


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