A Palladium NCP Pincer Complex as an Efficient Catalyst for Intramolecular Direct Arylation

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Abstract: CH functionalization is a convenient methodology with broad application in total synthesis and medicinal chemistry that provides the same products as already well established cross-coupling methodologies, but with the advantage of avoiding the use of metallic species such as Grignard, boron, silicon and tin compounds. Herein, we report an unprecedented palladium-catalyzed intramolecular direct arylation for the general access of phenanthridinones under very low catalyst loadings. With only 0.05 mol%, a palladium NCP pincer complex promotes efficiently the direct functionalization of a series of N-arylbenzanilides and N-arylsulfonamides which constitutes an effective, versatile and environmentally attractive procedure for the preparation of phenanthridinones, biaryl sulams and related heterocyclic derivatives.

Keywords: biaryl sulams; CH arylation; palladium; phenanthridinones; pincer complexes

1. Introduction

Palladium-catalyzed direct functionalization of C-H bonds has attracted significant attention over the last years, since the development of innovative, environmentally friendly and highly efficient synthetic strategies has become a priority in industry as well as in academia.[1] In this context, synthetic approaches based on palladium-catalyzed direct functionalization of arenes have been developed to synthesize phenanthridinone derivatives and related lactams, scaffolds found in many natural products which exhibit remarkable biological and pharmaceutical
properties. Though these methods have proven to be among the most versatile for the synthesis of such structures, they usually require big amounts of catalysts (2-10 mol%). Therefore, the development of a novel palladium-catalyzed approach for the direct functionalization of arenes using very low catalyst loadings would provide a cost-effective and environmentally very attractive procedure. Besides, such method would prevent metal contamination of the product which constitutes an interesting advantage regarding its potential application in medicinal chemistry.

Our group has applied palladium pincer-type complexes as very active catalysts or precatalysts (cat. loading ≤ 0.1 mol%) in a variety of chemical transformations. The power of pincer complexes lies in their unique balance of stability vs. reactivity, which confers them extraordinary catalytic performances. Thus, we envisaged that such palladium complexes would be the suitable tool to carry out a more efficient direct arylation of arenes with low catalyst loadings. Herein we report an unprecedented palladium-catalyzed intramolecular direct arylation of N-substituted o-bromobenzanilides and benzosulfonamides for the general access of phenanthridinones and related biaryl sultams using palladium pincer complex 1 under very low catalyst loadings.

2. Results and Discussion

A series of screening experiments were conducted by employing a set of palladium pincer complexes prepared by our group in only 0.1 mol% with N-methyl-N-phenyl-2-bromobenzamide 2a as substrate. In contrast with other bases/solvents assayed, the use of PCN catalyst 1 produced the desired phenanthridinone 3a in a 24% yield using KOAc as base in DMA (entry 1).

The effect of other solvents, the amount of base, solvent concentration, the addition of Brønsted acids, tetrabutylammonium bromide or cationic surfactants and, especially, the catalyst loadings was examined (entries 2-20). After careful experimentation, we succeeded to obtain phenanthridinone 3a in a very good yield (88%, entry 18) with only 0.05 mol% of palladium pincer complex 1 using 3 equiv of KOAc in a relatively concentrated solution of DMA-H2O (9:1, 0.3M). Moreover, a further decrease of the catalyst loading down to 0.01 mol% was also possible, affording desired phenanthridinone 3a although at the cost of lower yields (entries 19-20) even at longer reaction times.

To the best of our knowledge, these values represent the lowest catalyst loadings achieved so far for any biaryl coupling of an aryl halide with a nonfunctionalized arene. It should be also pointed out that the latter reactions were carried out in the air atmosphere with no effect on the reaction yield.

With the establishment of an optimal catalyst loading of 0.05 mol% as the most effective, the generality and scope of the reaction were studied. As summarized in Table 2, the functional tolerance of this procedure was observed by synthesizing various phenanthridinones and related heterocyclic quinolinones with good to excellent yields. The electronic nature of the substituents seemed to have a little effect on the product yields. Besides, the reaction with different aromatics as naphthalene and heterocycles proceeded selectively in this C(sp²)-H arylation (78-98%). Even sterically hindered substrates as
N-cyclohexyl amide 2d afforded the desired product 3d in an 86% yield.

We also investigated the applicability of this protocol to structurally related o-halo-N-aryl sulfonamides. Accordingly, a series of o-bromo-N-(hetero)arylbenzenesulfonamides 2i-s were readily prepared and reacted with only 0.05 mol% pincer catalyst 1 (Table 2). To our delight, the direct functionalization of N-(hetero)aryl sulfonamides with such low catalyst loadings afforded regioselectively the corresponding biaryl sultams.

Although the yields obtained in our case are in accordance with literature precedents and, on average, not as high as the ones obtained for the corresponding 6-membered ring sultams 3h-o, the significantly fewer amounts (0.05-0.09 mol%) of catalyst required turn our protocol into the most effective approach to benzoisothiazoloindoles and related heterocycles.

The measurement of the palladium content in benzothiazinodihydroquinoline 3n was conducted using IPC-MS and determined as low as 0.29 ppm. Therefore, our method also offers an additional benefit regarding the avoidance of scavenger resins or further purification steps in order to suppress metal contamination in the products.

Table 1. Selection of optimization assays.a)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst [Pd]</th>
<th>Base</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield [%]b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMF</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMPU</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMI</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>0.1 mol%</td>
<td>K2CO3</td>
<td>20 mol% benzoic acid</td>
<td>DMA</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>20 mol% BA^d)</td>
<td>DMA</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>25 mol% surfactant^e)</td>
<td>DMA/DMF</td>
<td>7-18</td>
</tr>
<tr>
<td>8</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>25 mol% TBAB</td>
<td>DMA</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA/o-xylene (1:1)</td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-THF (1:1)</td>
<td>51</td>
</tr>
<tr>
<td>11</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-H2O (9:1)</td>
<td>68</td>
</tr>
<tr>
<td>12</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-H2O (9:1)</td>
<td>57</td>
</tr>
<tr>
<td>13^f)</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-H2O (7.5:2.5)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>14^g)</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-H2O (9:1)</td>
<td>68</td>
</tr>
<tr>
<td>15^g)</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-H2O (9:1)</td>
<td>75</td>
</tr>
<tr>
<td>16^f,^g)</td>
<td>0.1 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-H2O (9:1)</td>
<td>83</td>
</tr>
<tr>
<td>17^g)</td>
<td>0.05 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-H2O (9:1)</td>
<td>70</td>
</tr>
<tr>
<td>18^f,^g)</td>
<td>0.05 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-H2O (9:1)</td>
<td>89 (88)</td>
</tr>
<tr>
<td>19^f,^g,^h)</td>
<td>0.03 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-H2O (9:1)</td>
<td>78</td>
</tr>
<tr>
<td>20^f,^g,^h)</td>
<td>0.01 mol%</td>
<td>KOAc</td>
<td>-</td>
<td>DMA-H2O (9:1)</td>
<td>57</td>
</tr>
</tbody>
</table>

a) Reaction conditions: 2a (1 equiv.), 1 (0.1 mol%), base (1.5 equiv.), solvent (0.06 M), 130°C, sealed tube, 20h under Ar. DMPU: N,N-Dimethylpropilpenourea; DMA: 1,3-Dimethyl-2-imidazolidinone. b) Determined by 1H NMR. Diethylene glycol dimethyl ether was used as internal standard. Isolated yield in parentheses. c) Starting material. d) BA: Brø nsted acids (pivalic, benzoic and p-toluensulfonic acid). e) CTAB: Hexadecyltrimethylammonium bromide; DDA: Dimethylidioctadecylammonium bromide. f) 3.0 eq. of KOAc g) Solvent (0.3 M) h) 48h. i) 96h.
Table 2. Intramolecular direct arylation of arenes.\textsuperscript{a)}

\begin{center}
\begin{tabular}{c c c c c c c}
\hline
 & & & & & & \\
\textbf{R} & \textbf{A} & \textbf{B} & \textbf{C} & \textbf{D} & \textbf{E} & \textbf{F} \\
\hline
3a & N & O & H & H & N & O \\
3b & N & O & H & H & N & O \\
3c & N & O & H & H & N & O \\
3d & N & O & H & H & N & O \\
3e & N & O & H & H & N & O \\
3f & N & O & H & H & N & O \\
3g & N & O & H & H & N & O \\
3h & N & O & H & H & N & O \\
3i & N & O & H & H & N & O \\
3j & N & O & H & H & N & O \\
3k & N & O & H & H & N & O \\
3l & N & O & H & H & N & O \\
3m & N & O & H & H & N & O \\
3n & N & O & H & H & N & O \\
3o & N & O & H & H & N & O \\
3p & N & O & H & H & N & O \\
3q & N & O & H & H & N & O \\
3r & N & O & H & H & N & O \\
3s & N & O & H & H & N & O \\
\hline
\end{tabular}
\end{center}

\textsuperscript{a)} Reaction conditions: 2 (1 equiv.), 1 (0.05 mol%), KOAc (3 equiv.), DMA-H$_2$O (9:1, 0.35M), 130°C, sealed tube, 20h under air. Isolated yields.\textsuperscript{b)} 0.09 mol% of 1 was used.

3. Materials and Methods

**General procedure for the direct arylation of arenes**

DMA (0.8 mL) and water (0.1 mL) were added to a heavy-wall pressure tube charged with substrate 2 (0.35 mmol) and KOAc (1.05 mmol) at room temperature. Then, a solution of pincer complex 1 in DMA (1.75 mM, 0.1 mL, 0.175 \mu mol of 1) was added, the tube was closed and it was heated to 130 °C for 20 h. After cooling, the crude was diluted with H$_2$O (2 mL) and washed with EtOAc (2 x 3 mL). The combined organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc in hexane) to give the desired product 3.

4. Conclusions

In summary, we have developed a method for the intramolecular direct arylation of arenes \textit{via} C-H bond functionalization at very low catalyst loadings. With only 0.05 mol%, palladium pincer complex 1 promotes efficiently the direct functionalization of a series of N-arylbenzanilides and N-arylsulfonamides providing a novel versatile and sustainable access to phenanthridinones, biaryl sultams and related heterocyclic derivatives.

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**Conflicts of Interest**

The authors declare no conflict of interest.

**References and Notes**


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