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Selective Para-C–H Alkynylation of Aniline Derivatives by Pd/S,O-Ligand Catalysis

Ke-Zuan Deng, Wen-Liang Jia, and M. Ángeles Fernández-Ibáñez

Abstract: Herein, we report a nondirected para-selective C–H alkynylation of aniline derivatives by a Pd/S,O-ligand-based catalyst. The reaction proceeds under mild conditions and is compatible with a variety of substituted anilines. The scalability and further derivatizations of the alkynylated products have been also demonstrated.

Introduction

The alkyne motif is a key functional group in organic chemistry due to its synthetic versatility. In addition, it is widely present in pharmaceuticals, biomolecules, natural products, and materials. Therefore, the development of methodologies that allow the introduction of this functional group is of great interest in synthesis. In this regard, one of the most common methods to obtain arylacetylenes is the Sonogashira coupling. Despite its popularity, this reaction suffers from the disadvantage of requiring prefunctionalized aryl halides. In the last decade, metal-catalyzed C–H functionalization has emerged as a greener alternative to traditional cross coupling since no prefunctionalization of starting materials is required. In this regard, metal-catalyzed C–H alkynylation reactions of arenes have been widely described. However, the majority of the reported methodologies rely on the use of directing groups (DGs), leading in most of the cases to the ortho-alkynylated products. Recently, a breakthrough was reported by the group of van Gemmeren on the Pd-catalyzed C–H alkynylation of non-directed arenes enabled by a dual ligand system. However, the C–H alkynylation of anilines, which are ubiquitous structural moieties in organic molecules, was not disclosed. As far as we know, only one report on the para-C–H alkynylation of anilines using Au catalyst has been reported by the Waser group (Scheme 1a). Hence, the development of new general methodologies that permit the remote C–H alkynylation of aniline derivatives is still needed. Herein, we report an efficient para-selective C–H alkynylation of a wide range of aniline derivatives by Pd/S,O-ligand based catalyst (Scheme 1b).

Results and Discussion

Recently, we discovered a new type of S,O-ligands, namely thioethercarboxylic acids, that enables Pd-catalyzed C–H olefination of simple arenes, thiophenes, anisole and aniline derivatives. So far, only the introduction of an olefin moiety was achieved using the Pd/S,O-ligand catalyst. However, taking into account the need to develop new methodologies for the remote C–H alkynylation of aniline derivatives, we decided to investigate if the Pd/S,O-ligand catalyst was also suitable for the introduction of alkyne functionalities.

We started our investigations using N,N-dibenzylaniline 1a and 1-iodo-2-(triisopropylsilyl)acetylene as model substrates in the presence of Pd(OAc)$_2$, 3-methyl-2-(phenylthio)butanoic acid as S,O-ligand and AgOAc using a sealed tube. After an extensive screening of reaction conditions including solvents, silver salts, temperatures, Pd and alkynyl sources and S,O-ligands, optimal results were obtained using 1-iodo-2-(tert-butylidiphenylsilyl)acetylene (2 equiv) as alkynyl source, Pd(OAc)$_2$/S,O-ligand L1 (10 mol%) as catalyst, in the presence of AgOAc (2 equiv) in chloroform (0.2 M) at 80 °C (see Supporting Information). Under these conditions, we obtained the desired para-alkynylated product 2a in 58% isolated yield. It is worth mentioning that the reaction proceeds with perfect para-
selectivity as no other regioisomers were detected in the crude mixture.\(^{[13]}\)

With the optimal alkylation conditions in hand, we explored the C–H alkylation reaction using different substituted anilines (Table 1). First, we evaluated meta-halogenated N,N-dibenzylanilines. The reaction of N,N-dibenzyl-3-fluoroaniline (1b) with 1-iodo-2-(3-butyldiphenylsilyl)acetylene provided the desired product 2b in 69% isolated yield with perfect para-selectivity. Replacing the TBDPS protecting group by TIPS gave the product 2c in 62% yield. When 3-chloro- and 3-bromo-anilines were used, 58% isolated yield of the desired products 2d and 2e were obtained. Then, when the reaction was performed with 3-methyl- methoxy and -phenoxy N,N-dibenzylanilines, the para-alkynylated products 2f–h were isolated in synthetically useful yields (42–69%). In these reactions, some decomposition of the starting or/and final anilines was observed, especially for the aniline bearing the methoxy group. Next, we switched our attention to ortho-substituted anilines. Based on our previous experience that only ortho-substituted secondary anilines are suitable substrates in these C–H functionalization reactions,\(^{[11d]}\) we performed the reactions using N-benzyl anilines. We observed that ortho-substituted anilines bearing electron donating substituents were prone to decomposition under the reaction conditions used. Nevertheless, to our delight, the less reactive o-CO₂Me-substituted N-benzyl aniline 1i provided the desired product in 43% isolated yield with perfect para-selectivity. Then, we evaluated a variety of disubstituted N-benzyl anilines. Disubstituted anilines with an ortho-methyl ester group and Me₂N–OMe and –F substituent at the meta-position underwent C–H alkylation to provide only the para-alkynylated products 2j–2l in synthetically useful yields (37–50%). N-Benzyl-o-chlorom-(methoxy)aniline (1m) was also a suitable substrate providing the para-alkynylated product in 40% yield. To highlight the key role of the S,O-ligand in this transformation, we performed the C–H alkylation in the absence of the S,O-ligand for each substrate (Table 1). As expected, no alkynylated or traces of product were obtained, highlighting the crucial role of the S,O-ligand in the reaction. In comparison with the previously reported methodology by Waser et al., this methodology is clearly more suitable for anilines bearing electron withdrawing groups while higher yields are obtained with anilines bearing electron donating substituents using Waser’s methodology. Next, we proved the practicability of the reaction by performing the C–H alkylation of N,N-dibenzyl-3-fluoroaniline (1b) on a 3.0 mmol scale. Under standard reaction conditions, the para-alkynylated product 2b was obtained in 76% isolated yield.

After proving the efficiency of the Pd/S,O-ligand catalyst in anilines bearing both electron donating and withdrawing groups, we studied the effect on the reaction of different substituents attached to the nitrogen atom (Table 2). 3-Fluoro N,N-dimethyl- and N,N-diethylaniline (1n–1o) were alkynylated in 57% and 68% isolated yield, respectively. Interestingly, only the para-alkynylation of the 3-fluorophenyl ring when using 3-fluoro-N-methyl-N-phenylaniline (1p) was detected, showing the beneficial effect of the fluorine substituent in the reaction. The reaction of N-(3-fluorophenyl)pyrrolidine (1q) and N-(3-fluorophenyl)morpholine (1r) furnished the para-alkynylated products in synthetically useful yields (42–51%). Next, we performed the reaction with the unprotected 8-acetyltetrahydroquinoline (1s) and the bioactive spiro-tetrahydroquinoline derivative 1t.\(^{[14]}\) To our delight, both substrates were compatible with the reaction conditions, providing the alkynylated products in 49% and 50% isolated yield, respectively.

Finally, we proved the synthetic utility of the alkynylated products obtained via Pd-catalyzed C–H alkylation reactions as building blocks by performing further derivatization reactions (Scheme 2). The deprotection of 2b was conducted using TBAF/THF providing the desilylation product 3 in an excellent

Table 1. para-C–H alkylation of N-benzylaniline.\(^{[4]}\)

<table>
<thead>
<tr>
<th>Aniline</th>
<th>TBDPS</th>
<th>TIPS</th>
<th>2b</th>
<th>2c</th>
<th>2d</th>
<th>2e</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBn²</td>
<td>2a, 58%</td>
<td>3%</td>
<td>69%, 76%</td>
<td>0%</td>
<td>62%</td>
<td>0%</td>
</tr>
<tr>
<td>NBn²</td>
<td>2b, 69%</td>
<td>76%</td>
<td>0%</td>
<td>0%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>NBn²</td>
<td>2c, 62%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>NBn²</td>
<td>2d, 58%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>NBn²</td>
<td>2e, 58%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>NBn²</td>
<td>2f, 51%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>NBn²</td>
<td>2g, 42%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>NBn²</td>
<td>2h, 69%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

[a] ±H NMR yields of parallel reactions without ligands are given in black. [b] ±H NMR yields were determined from the crude mixtures using CH₃Br₂ as an internal standard. [c] 3.0 mmol scale. [d] 1.0 equiv of alkyne substrate were used. [e] 1.0 equiv of alkyne source and AgOAc were used. [f] 2.0 equiv of aniline substrate and AgOAc were used. [g] 100 °C.

yield of 92% (Scheme 2a). The treatment of the obtained terminal alkyne 3 with iodobenzene under typical Sonogashira coupling conditions led to diphenylethyne 4 in 80% yield. Moreover, the terminal alkyne 3 was subjected to a click reaction to provide the triazole 5 in 66% yield. To further prove the synthetic value of our methodology, we performed the derivatization of the \( m \)-bromo substituted alkynylated aniline 2e. Thus, the coupling of 2e with PhB(OH)2 and morpholine using a Pd catalyst, furnished the coupling products in 52% and 80% isolated yield, respectively (Scheme 2b).

**Conclusion**

In conclusion, we have developed a general protocol for nondirected \( para \)-selective \( C-H \) alkylation of aniline derivatives by Pd/5,S,O-ligand catalysis. The reaction proceeds under mild conditions with perfect \( para \)-selectivity providing the alkynylated anilines in synthetically useful yields. A wide number of \( ortho \) and \( meta \) substituted anilines bearing both electron donating and withdrawing substituents are compatible with the catalytic system. Anilines with different substituents attached to the nitrogen atom as well as tetrahydroquinolines are alkynylated in good yields. The methodology is operationally simple and scalable. The synthetic versatility of the functionalized products was shown by further derivatization of the alkynylated anilines.

**Acknowledgements**

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**Conflict of Interest**

The authors declare no conflict of interest.

**Data Availability Statement**

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** aniline · alkylation · \( C-H \) activation · palladium · \( S,O\)-ligand

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**Table 2.** \( para-C-H \) alkylation of \( N,N \)-disubstituted anilines and tetrahydroquinolines.

<table>
<thead>
<tr>
<th>N,N-disubstituted anilines</th>
<th>( \text{Pd(OAc)}_2 ) (10 mol%)</th>
<th>( S,O )-ligand ( L1 ) (10 mol%)</th>
<th>( \text{AgOAc} ) (2.0 equiv)</th>
<th>CHCl(_3) (0.2 M)</th>
<th>80 °C, 16 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{NR}^1 \text{R}^2 )</td>
<td>( \text{TBDPS} )</td>
<td>( \text{TBDPS} )</td>
<td>( \text{TBDPS} )</td>
<td>( \text{TBDPS} )</td>
<td>( \text{TBDPS} )</td>
</tr>
<tr>
<td>( \text{NMe}_2 )</td>
<td>2a, 57%</td>
<td>2a, 49%</td>
<td>2a, 49%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>( \text{NEt}_3 )</td>
<td>2b, 68%</td>
<td>2b, 68%</td>
<td>2b, 68%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>( \text{Ph} )</td>
<td>2c, 42%</td>
<td>2c, 42%</td>
<td>2c, 42%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>( \text{tetracycloquinolines} )</td>
<td>2d, 51%</td>
<td>2d, 51%</td>
<td>2d, 51%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>( \text{N} )</td>
<td>2e, 44%</td>
<td>2e, 44%</td>
<td>2e, 44%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

[a] \( ^1 \text{H} \) NMR yields of parallel reactions without ligands are given in black. \( ^1 \text{H} \) NMR yields were determined from the crude mixtures using CH\(_2\)Br\(_2\) as an internal standard. [b] 1.0 equiv of alkyne source, 1.0 equiv of AgOAc and 2.0 equiv of aniline substrate were used.

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**Scheme 2.** Synthetic derivatizations of the alkynylated products.