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Naksomboon, K.; Poater, J.; Bickelhaupt, F.M.; Fernández-Ibáñez, M.A.

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**para-Selective C–H Olefination of Aniline Derivatives via Pd/S,O-Ligand Catalysis**

Kanat Nakomboon, ‡ Jordi Poater, ‡,.§ F. Matthias Bickelhaupt, ‡,¶§ and Ángeles Fernández-Ibáñez ‡,*

Abstract: Herein we report a highly para-selective C–H olefination of aniline derivatives by a Pd/S,O-ligand-based catalyst. The reaction proceeds under mild reaction conditions with high efficiency and broad substrate scope, including mono-, di-, and trisubstituted tertiary, secondary, and primary anilines. The S,O-ligand is responsible for the dramatic improvements in substrate scope and the high para-selectivity observed. This methodology is operationally simple, scalable, and can be performed under aerobic conditions.

1. INTRODUCTION

Aromatic amines are ubiquitous structural motifs in natural products, pharmaceuticals, fluorescent dyes, and organic functional materials.‡ As a consequence, the selective functionalization of anilines is of great interest in organic chemistry. Historically, Friedel–Crafts reactions of aniline derivatives are problematic, as has been stated in classical textbooks. Two cross couplings are effective reactions for the functionalization of aromatic amines, however, these protocols suffer from the disadvantage of requiring prefunctionalized starting materials. In the last decades, metal-catalyzed C–H functionalization reactions have become a powerful tool to efficiently functionalize organic molecules. The vast majority of C–H functionalization reactions of aniline derivatives rely on the use of directing groups attached to the nitrogen atom, which results in the ortho-functionalized products. However, selective C–H functionalization reactions of aniline derivatives at remote positions are rare. Six in the particular case of metal-catalyzed para-selective C–H functionalization of anilines, the reported transformations are limited to unsubstituted anilines or to anilines bearing electron-donating groups. Few exceptions to this trend have been reported. For instance, anilides with an ester group or halogen atom have been para-difluoromethylated using a Ru(II)-catalyst. Also, a highly para-selective copper(II)-catalyzed arylation of electron-rich and -poor anilines was described by Gaunt and co-workers. In the context of Pd-catalyzed para-C–H olefination of anilines, only two examples using unsubstituted tertiary anilines have been reported. In the example described by Ishii et al., 7.5 equiv of tertiary aniline are necessary to obtain the olefinated products in good yields and para-selectivities using Pd/HPMoV as catalyst and 2,4,6-trimethylbenzoic acid as an additive. In the second example, the para-olefination of unsubstituted N,N-dialkylanilines using Pd as catalyst, Cu as oxidant, and a mixture of DCE/HOAc as solvent is reported. Therefore, a general strategy for para-selective C–H olefination of aromatic amines is still elusive. Herein, we report a highly efficient para-selective C–H olefination of aniline derivatives promoted by a Pd/S,O-ligand based catalyst. The reaction proceeds under mild conditions with a broad range of mono-, di-, and trisubstituted tertiary, secondary, and primary anilines. Remarkably, anilines bearing several electron withdrawing groups are also compatible, affording the para-olefinated products in good yields. In addition, this para-selective C–H olefination of anilines is also easily scalable and is compatible with the use of oxygen as the only oxidant, which are important features for industrial applications. The S,O-ligand is responsible for the...
dramatic improvements in substrate scope and the high para-selectivity observed.

Recently, we have discovered that bidentate S,O-ligands are capable of promoting Pd-catalyzed C–H olefination reactions of nondirected arenes. In these reactions, the site-selectivity was mainly dictated by the substrate and controlled by electronic factors, with preferential functionalization at the most electron-rich position in the arene. We found out that besides accelerating the reaction, the presence of the S,O-ligand influences the site-selectivity of the process. With this in mind, we speculated that using our Pd/S,O-ligand catalyst, both the reactivity and the site-selectivity of the C–H olefination of aniline derivatives could be enhanced.

2. RESULTS AND DISCUSSION

2.1. Scope of Pd/S,O-Ligand Catalyzed C–H Olefination of Aniline Derivatives. Initially, we applied our standard conditions for the C–H olefination of nondirected arenes (5 mol % of Pd(OAc)₂, 5 mol % of 3-methyl-2-(phenylthio)butanoic acid (L), 10 equiv of arene, and 1 equiv of PhCO₂Bu as oxidant in AcOH at 100 °C for 6 h) on the model substrate, N,N-Dimethylaniline (1a). Unfortunately, no olefinated product was observed under these conditions. Different reaction parameters, including solvents, temperatures, reaction stoichiometries, oxidants, concentrations, and ligands were screened (see the Supporting Information). We were pleased to find out that the reaction of N,N-Dimethylaniline (1a, 1 equiv) with ethyl acrylate, using the Pd/S,O-ligand (L) as catalyst, in DCE at 40 °C, furnished the olefinated product 3a in 81% NMR yield with excellent para-selectivity (p:o > 19:1) (71% isolated yield of the para-olefinated product 3a, Scheme 2). In contrast, the reaction without ligand, under the same conditions, gave the olefinated product 3a in 18% NMR yield as a mixture of the 3 possible isomers (o:m:p = 1:1:16).

To investigate the substrate scope of this transformation, various aniline derivatives were examined (Table 1). We first explored the olefination reaction of several tertiary aniline derivatives. N,N-Diethyl-, N,N-dibenzylaniline, and 1-phenylpyrrolidine (1b−1d) were olefinated in excellent yield (73–85%) and excellent selectivity toward their para positions. Good yields and slightly deteriorated selectivities were observed using 4-phenylmorpholine (1e) and N-methylidiphe-
ynilamine (1f). Julolidine reacted to form only the para-olefinated product 3g in 60% isolated yield. Having proved the compatibility of the method with a variety of tertiary aniline derivatives, different meta-substituted N,N-dimethylanilines were then tested. The reaction of m-methyl N,N-dimethylaniline (1h) provided the olefinated product 3h in good yield (70%) and para-selectivity (>10:1). Good yield (75%) and moderate para-selectivity was observed in the reaction of the m-phenoxymethyl N,N-dimethylaniline (1i). In contrast, the reaction of the m-phenoxymethyl N,N-dimethylaniline (1j) exhibited a perfect para-selectivity, obtaining the product 3j in 66% isolated yield. The corresponding para-olefinated products of N,N-dimethylanilines derivatives bearing electron withdrawing substituents such as F, Cl, and CO₂Me (1k-m) were obtained in good yields (51–65%). Similarly, the reaction tolerated two fluorine atoms at the meta position of the aniline, providing the para-olefinated product 3n in 42% isolated yield. Interestingly, and in accordance with the high para-selectivity observed in these transformations, only 3% of the ortho-olefinated product was detected when using p-methyl N,N-dimethylaniline (1o). To extend the substrate scope of the reaction, we tested the reaction of p-methyl N,N-dimethylaniline (1p) under standard reaction conditions, but only trace amounts of product were detected by 1H NMR spectroscopy.¹¹

Alternatively, N-benzyl ortho-substituted aniline derivatives were efficiently para-olefinated using our Pd/S,O-ligand based catalyst (Table 2). The reaction of o-Me-, OMe-, Cl-, CF₃-, CO₂Me-, and COMe-substituted N-benzyl aniline derivatives 1q-1v exhibited perfect para-selectivities, providing the para-olefinated products in good yields (47–70%). Only traces amounts of the C–H olefinated product occurring at the ortho position of the benzene ring of the benzyl group were detected. In contrast, this byproduct was formed in greater quantity when the reactions were performed without the ligand (see the Supporting Information).

After proving the efficiency of the new catalytic system in anilines bearing both electron donating and withdrawing groups, we evaluated a variety of di- and trisubstituted N-benzylaniline derivatives. Disubstituted anilines with an ortho methyl ester group and different substituents at the meta-position (i.e., F, OMe, and Me) underwent C–H olefination to provide the para-olefinated products 3w-3y in good yields (57–75%). N-Benzyl-m-methyl-o-(trifluoromethyl)aniline (1z) and o-chloro-m-methoxyaniline (1aa) were also compatible with this system, providing the para-olefinated products in 53% and 52% isolated yield, respectively. Slightly higher yields for the olefinated products 3ab and 3ac were obtained when 2,3-dichloro- and 2,3-dichloro aniline derivatives were used. The reaction of the trisubstituted o-methyl ester m-m′-difluoroaniline derivative provided the para-olefinated product 3ad in 60% isolated yield.

Finally, we studied the compatibility of the current catalytic system with primary anilines (Table 3). We observed that the efficiency of the reaction is highly dependent on the substituents attached to the aromatic ring. The reaction of ortho-disubstituted anilines bearing two electron donating groups provided the olefinated product in low yields. In these reactions, we detected the formation of the oxidative amination product (see the Supporting Information for further details).¹² To our delight, the olefinated products were obtained in high yields and with perfect para-selectivities with ortho-disubstituted anilines bearing one ester group at the ortho-position. Thus, different substituents at the other ortho-position such as CO₂Me, Me, OMe, and Cl were compatible in the reaction, providing the olefinated products 3ae-3ah in good isolated yields (64–71%). The reaction of the trisubstituted aniline 1ai bearing two fluorine atoms and a methyl ester furnished the

Table 2. para-Selective C–H Olefination of Primary Anilines

<table>
<thead>
<tr>
<th>Aniline</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>3b</td>
<td>62</td>
<td>80</td>
</tr>
<tr>
<td>3c</td>
<td>3d</td>
<td>62</td>
<td>80</td>
</tr>
<tr>
<td>3e</td>
<td>3f</td>
<td>62</td>
<td>80</td>
</tr>
<tr>
<td>3g</td>
<td>3h</td>
<td>62</td>
<td>80</td>
</tr>
</tbody>
</table>

*Yields and selectivities were determined by 1H NMR analysis of the crude mixture using hexafluorobenzene as an internal standard.

Yields and selectivities were determined by 1H NMR analysis of the crude mixture using CH₃Br₂ as an internal standard. Isolated yields of p-isomer were given in the square bracket. “1.5 Equiv of aniline derivative was used.”

1.5 Equiv of aniline derivative was used.
olefinated aniline 3ai in 70% isolated yield. A fair yield (45%) was obtained in the reaction of the disubstituted (α-CF₃ and α-OMe) aniline.

It is worth mentioning that in all these reactions (Tables 1, 2, and 3), the presence of the S,O-ligand is crucial to achieve good yield and high para-selectivity (see the Supporting Information for the results of the reactions in the absence of the S,O-ligand).

Next, we investigated the scope of olefins as depicted in Table 4. The reaction of N,N-diethylaniline with methyl, cyclohexyl, and phenyl acrylates provided the products in high yield (85–96%) and selectivity. α-Methylene-γ-butyrolactone afforded compound 4d in excellent yield as a mixture of 4dA and 4dB in a 1.4 to 1 ratio. Likewise, other activated olefins (i.e., vinyl amide, methyl vinyl ketone, vinyl phosphonate and vinyl sulfonate) were also employed to provide products 4e–4h in good yields.

Scheme 3. C–H Olefination of N,N-Dimethylaniline under Active Conditions

Table 4. Scope of Olefins

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Yields and selectivities (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et₂N=C=O</td>
<td>95% (93%)</td>
</tr>
<tr>
<td>Ph₂C=C=O</td>
<td>95% (93%)</td>
</tr>
<tr>
<td>N,N-diethylaniline</td>
<td>95% (93%)</td>
</tr>
<tr>
<td>N,N-diethylaniline</td>
<td>95% (93%)</td>
</tr>
<tr>
<td>N,N-diethylaniline</td>
<td>95% (93%)</td>
</tr>
</tbody>
</table>

*Yields and selectivities were determined by 1H NMR analysis of the crude mixture using CH₂Br₂ as an internal standard. Isolated yields of p-isomer were given in square bracket.*

To prove the applicability of the present catalytic system, a half-gram-scale reaction of N,N-dimethylaniline (1a) was conducted to afford 3a in comparable yield (64%) to that of the original value (for further details, see the Supporting Information). In addition, we explored the possibility of replacing PhCO₂Bu with oxygen (Scheme 3). The reaction of N,N-dimethylaniline (1a) under otherwise identical conditions using a balloon of oxygen showed the formation of the olefinated product 3a in 15% yield. To our delight, the reaction using 2 bar of oxygen provided the desired product in 57% yield in good para-selectivity. These results show the potential of this methodology to be implemented in the chemical industry.

2.2. Comparison of the Pd/S,O-Ligand Catalytic System with the Reported Catalytic Systems for the para-C–H Olefination of Anilines. As mentioned in the Introduction, only two examples were reported for the Pd-catalyzed para-C–H olefination of anilines. To demonstrate that this catalytic system is a unique method to olefinate a broad range of anilines, we compared our catalytic system with previously described protocols. We performed the reaction of N,N-dimethylaniline with methyl acrylate under the conditions described by Moghaddam et al.: Pd(OAc)₂ (5 mol %) and Cu(OAc)₂ (1.5 equiv) in a mixture of DCE/HOAc (1:1) at 60 °C; however, in our hands only a trace amount of olefinated product was detected by 1H NMR spectroscopy. We then tested different anilines under the conditions described by Obora and Ishii using 7.5 equiv of aniline, Pd(OAc)₂ (5 mol %), H₂PMo₉V₃O₄₀₃⁴H₂O (0.5 mol %), and 0.5 equiv of 2,4,6-trimethylbenzoic acid in DMF (Table 5). The reaction of N,N-dimethylaniline under these conditions gave the olefinated product in 70% yield and high para-selectivity (10.7:1). Remarkably, under Ishii’s conditions, only 24% ¹H NMR yield and moderate para-selectivity (4:6:1) was observed using Ishii’s conditions. Using our catalytic system, we obtained the olefinated product 3h in 70% yield and high para-selectivity (10.7:1). Remarkably, under Ishii’s conditions, no reaction or only trace amounts of product was obtained.

Table 5. Comparison of Pd/S,O-Ligand Catalyst with Ishii’s Catalyst

<table>
<thead>
<tr>
<th>Substrates</th>
<th>No ligand*</th>
<th>L⁺</th>
<th>Ishii’s conditions⁺⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂N=CH₂</td>
<td>18% (p:m = 10:1)</td>
<td>81% (p:m = 10:1)</td>
<td>80% (p:m = 13:3:1)</td>
</tr>
<tr>
<td>Me₂N=CH₂</td>
<td>11% (p:m others = 2.7:1)</td>
<td>70% (p:m others = 2.7:1)</td>
<td>26% (p:m others = 4:6:1)</td>
</tr>
<tr>
<td>Me₂N=CH₂</td>
<td>17% (p:m others = 1.8:1)</td>
<td>81% (p:m others = 1.8:1)</td>
<td>9% (p:m others = 2.7:1)</td>
</tr>
<tr>
<td>Me₂N=CH₂</td>
<td>27%</td>
<td>70%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Yields and selectivities were determined by ¹H NMR analysis of the crude mixture using CH₂Br₂ as an internal standard. Yields and site selectivities reported previously in ref 7b. NR = no reaction.*

N,N-dimethylaniline under these conditions gave the olefinated product in good yield and with slightly lower para-selectivity than using our catalytic system. When we performed the reaction of m-methyl N,N-dimethylaniline (1h), only 24% ¹H NMR yield and moderate para-selectivity (4:6:1) was observed using Ishii’s conditions. Using our catalytic system, we obtained the olefinated product 3h in 70% yield and high para-selectivity (10.7:1). Remarkably, under Ishii’s conditions, no reaction or only trace amounts of product was detected when m-methoxy- or m-methyl ester N,N-dimethylaniline (1i or 1m) were employed. Similarly, the reaction of N-benzyl ortho-substituted anilines (1q and 1u) under Ishii’s conditions provided only a trace amount of product in contrast to our
catalytic system that furnished the olefinated products in good yields and perfect para-selectivities. Overall, Ishii’s conditions are suitable for the olefination of unsubstituted tertiary anilines, and therefore, we can confirm that our catalytic system based on the Pd/S,O-ligand is at present the only efficient protocol for the direct C–H olefination of a broad range of anilines.

2.3. Explanation of the Difference in Reactivity of Tertiary and Secondary Anilines Respect to the ortho-Substituent. As shown in Table 1, the reaction of o-methyl N,N-dimethylaniline (1p) under optimal conditions provided only trace amounts of olefinated product. In contrast, N-benzyl ortho-substituted anilines were efficiently para-olefinated using our Pd/S,O-ligand based catalyst (Table 2). The lack of reactivity of ortho-substituted N,N-dialkylanilines in aromatic electrophilic substitution reactions has been observed before.

It has been postulated that the ortho-substituent clashes with the N-methyl group of the N,N-dimethylaniline forcing the nitrogen to twist out of the plane with the aromatic ring, reducing the conjugation of the nitrogen lone pair and therefore deactivating the aniline derivative toward electrophilic substitution. To corroborate this, we calculated the torsion angle and the Voronoi deformation density (VDD) charges of 1p and 1q (Chart 1) at dispersion-corrected density functional theory (DFT) level (see the Supporting Information).

In the case of o-methyl N-benzyl aniline (1q), the H of the NHBn almost remains in the plane (δ = 18°) and points toward the o-methyl group. In contrast, one of the Me groups of the NMe2 of 1p is twisted out of the plane (δ = 69°) to avoid the interaction with the methyl group at the ortho position. As a consequence, the C atoms at the ortho and para positions of 1q (–85 and –88 me., respectively) are more negatively charged than the equivalent ones in 1p (–77 and –74 me., respectively). Therefore, the lack of reactivity observed in o-substituted N,N-dialkylanilines is a direct consequence of the lower nucleophilicity of these anilines compared with unsubstituted N,N-dialkylanilines or with o-substituted N-benzyl anilines.

2.4. Preliminary Mechanistic Investigations. To gain some insights into the role of the S,O-ligand in this transformation, we conducted some additional experiments (Scheme 4). We considered 2 different scenarios to explain the observed acceleration in the presence of the ligand: (i) the ligand causes a change in the mechanism of C–H bond cleavage or (ii) the ligand accelerates the rate-limiting step.

First, we determined the hydrogen/deuterium isotopic effect in the reaction with and without the ligand (Scheme 4a). Without the ligand, we observed a kH/kD of 8.5 and in the presence of the S,O-ligand (L) a kH/kD of 6.2. The observed primary kinetic isotopic effect suggests that the C–H bond cleavage is the turnover-limiting step in both cases. Furthermore, we performed one-pot intermolecular competition experiments between an electron-poor aniline, namely N,N-dimethyl-3-(trifluoromethyl)aniline (1ak), and an electron rich-aniline, namely N,N,3-trimethylaniline (1h) (Scheme 4b). We found out that in both cases, the most electron-rich aniline 1h reacted preferentially. These results are consistent with two possible mechanisms: (i) the reaction proceeds via an electrophilic palladation mechanism with the deprotonation of the Wheland intermediate being the rate-limiting step or (ii) the reaction proceeds via a base-assisted internal electrophilic-type substitution (BIES) mechanism.

At present, we cannot rule out either mechanism but it seems reasonable to postulate that the reaction proceeds via the same mechanism with and without the ligand and that the S,O-ligand accelerates the C–H bond cleavage, which is the rate-limiting step.

3. CONCLUSION

In conclusion, we have developed the first general para-selective C–H olefination of aniline derivatives by Pd/S,O-ligand catalysis. The reaction proceeds under mild reaction conditions with a broad range of anilines, including mono-, di-, and trisubstituted anilines bearing electron-donating and -withdrawing groups. In total, 42 aniline derivatives underwent para-selective C–H olefination in good yields using the developed methodology. We have also shown that it is possible to use oxygen as the only oxidant and that this methodology is operationally simple and scalable. The S,O-ligand is responsible for the dramatic improvements in substrate scope and the high para-selectivity observed in this transformation. Preliminary mechanistic studies suggest that the ligand promotes the C–H bond cleavage, which is the rate-limiting step. Further applications and mechanistic studies are currently ongoing in our laboratory.


(11) Other N,N-dimethylaniline derivatives with different substituents at the ortho-position were evaluated under standard reaction conditions. In none of these reactions was observed the formation of the para-olefinated product in synthetically useful yields.


(14) In electrochemical aromatic substitution reactions, including electrochemical palladation, the formation of the Wheland intermediate is, in general, the rate-limiting step, providing small KIE values. However, in some cases, large KIE values have been reported where the rate of deprotonation is slow. See: Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Ligand-Accelerated C–H Activation Reactions: Evidence for a Switch of Mechanism. J. Am. Chem. Soc. 2010, 132, 14137–14151 and references therein .