Meta-C-H arylation of aniline derivatives via palladium/S,O-ligand/norbornene cooperative catalysis

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meta-C–H Arylation of Aniline Derivatives via Palladium/ S,O-Ligand/Norbornene Cooperative Catalysis

Verena Sukowski, Manuela van Borselen, Simon Mathew, Bas de Bruin, and M. Ángeles Fernández-Ibáñez*

Abstract: Aromatic amines are ubiquitous moieties in organic molecules and their direct functionalization is of great interest in many research areas due to their prevalence in pharmaceuticals and organic electronics. While several synthetic tools exist for the ortho- and para-functionalization of anilines, the functionalization of the less reactive meta-position is not easy to achieve with current methods. To date, the meta-C–H arylation of aniline derivatives has been restricted to either the use of directing groups & templates, or their transformation into anilides & quaternary anilinium salts. Herein, we report the first general and efficient meta-C–H arylation of non-directed aniline derivatives via cooperative catalysis with a palladium–S,O-ligand–norbornene system. The reaction proceeds under mild conditions with a wide range of aniline derivatives and aryl iodides, while being operationally simple and scalable. Our preliminary mechanistic investigation—including the isolation of several palladium complexes and deuterium experiments—reveal useful insights into the substituent-effects of both the aniline-substrate and the norbornene-mediator during the meta-C–H activation step.

Introduction

Aromatic amines are ubiquitous moieties in organic molecules and can be found in natural products, pharmaceutical, agrochemicals and material sciences. Thus, the development of efficient methods for their preparation and diversification continues to attract a high-level of interest. Transition-metal catalyzed C–H bond activation has emerged as a promising method to functionalize organic molecules due to its high efficiency and good atom economy. In this regard, the majority of C–H functionalization reactions for aniline derivatives rely on the use of directing groups that generally provide ortho-functionalized products. On the other hand, the para-C–H functionalization of anilines has been accomplished by exploiting the intrinsic ionic and electronic reactivity of this position in non-directed approaches. However, meta-functionalization of anilines derivatives remains a challenge and only few strategies are reported (Scheme 1a). Rationally designed templates for Pd-catalyzed meta-C–H functionalization of anilides derivatives have been described by several authors following the pioneering work of Yu. Non-covalent interactions have enabled the Ir-catalyzed meta-C–H borylation of anilides and quaternary anilinium salts. Recently, the group of van Gemmeren described one example for palladium catalyzed meta-C–H olefination of a quaternary anilinium salt using a similar non-covalent approach. The meta-C–H arylation of anilides combining a copper catalyst and diphenyliodonium salts was reported by the group of Gaunt. Similarly, other procedures that rely on the transformation of the amine moiety into an electron withdrawing group were described with moderate meta-selectivities and/or narrow substrate scope. Alternatively, ortho-directing groups were employed for the meta-C–H alkylation and sulfonation of anilines by ruthenium catalysis.

Scheme 1. meta-C–H Functionalization of anilines.
where ortho-\(\text{C-H}\) activation takes place followed by a single electron transfer process at the meta-position.\[14\] In addition, the use of ortho-directing groups in combination with a norbornene (NBE) mediator was introduced by the group of Yu for the meta-\(\text{C-H}\) functionalization of Boc-protected anilines.\[16-18\] To date, no methodologies for the direct meta-\(\text{C-H}\) functionalization of non-directed anilines, without their transformation into anilides or quaternary anilinium salts, have been reported. Therefore, the development of a direct method that allows the meta-\(\text{C-H}\) arylation of aniline derivatives, without the need to add extra synthetic steps such as the use of directing groups or the derivatization of the aniline, will provide an invaluable synthetic tool for late-stage diversification of biological active compounds. In addition, such methodology will offer the opportunity to functionalize the unconventional meta-position of aromatic amines, providing access to potentially new molecules with improve properties.

Recently, ligand-enabled non-directed C-\(\text{H}\) activation in combination with NBE mediators has emerged as a valuable tool to functionalize the less electronically favored position of arenes with high selectivity.\[16-18\] In this context, in 2019 a seminal work on the meta-\(\text{C-H}\) arylation of electron-rich alkoxynores were reported by the group of Yu.\[19\] In this seminal publication, limitations of the catalytic system were noted, such as the lack of reactivity of anilines bearing electron withdrawing substituents and anilines protected with electron withdrawing groups (such as Boc, Cbz or Ts) and the instability of tertiary anilines under the reaction conditions.

In 2017, our group has disclosed a new catalytic system based on Pd/S,O-ligand, capable of promoting Pd-catalyzed C-\(\text{H}\) arylation of aniline and anilide derivatives bearing several electron withdrawing substituents, substrates that were unreactive using other catalytic systems. In 2022, taking into consideration the high catalytic activity of our Pd/S,O-ligand system, we reported a methodology based on Pd/S,O-ligand/NBE cooperative catalyst for the meta-\(\text{C-H}\) arylation of aniline derivatives.\[20\] The new methodology overcomes the previously mentioned limitations (see above), allowing for example the functionalization of a wide number of anilide derivatives, including those with several electron withdrawing substituents. Therefore, taking into account that the Pd/S,O-ligand catalyst was suitable for the C-\(\text{H}\) olefination of a wide range of aromatic amines\[4\] and is compatible with the norbornene mediator,\[20\] we hypothesized that we could develop the first meta-\(\text{C-H}\) arylation of undervatalized anilines using simple aryl iodides as coupling partners. Herein, we report a general and efficient meta-\(\text{C-H}\) arylation of non-directed aniline derivatives via Pd/S,O-ligand/norbornene cooperative catalysis (Scheme 1b). The reaction proceeds under mild reaction conditions with a wide range of anilines, including unstable tertiary anilines or less reactive Boc-protected anilines. Ortho-substituted anilines are efficiently arylated by overcoming the ortho-constraint, through simple selection of the appropriate NBE mediator. Remarkably, by the judicious choice of the S,O-ligand and NBE mediator a wide range of aryl iodides — including those lacking electron withdrawing ortho-substitution — and other Pd/NBE cooperative catalysis\[17a,18,21\] were investigated.

### Results and Discussion

Initially, we performed the C-\(\text{H}\) arylation using N,N-dibenzyl-3-methylaniline (1b) as model substrate, 2.0 equiv. of methyl 4-iodobenzoate (2a) in the presence of 10 mol % of Pd(OAc)\(_2\), and the S,O-ligand L1, 1.0 equiv. of NBE N1 and 2.0 equiv. of AgOAc at 70 °C (Table 1a). Under these conditions, only 12 % of the desired meta-arylated product was detected by \(^1\)H NMR along with the products coming from the decomposition of the aniline. Therefore, we decided to test the reaction with aryl iodides bearing an ortho-coordinating group, such as methyl 2-iodobenzoate (2b), which are known to be more reactive in these transformations probably by promoting the oxidative addition step.\[17a,18,21,22\]

To our delight, under these conditions 48 % \(^1\)H NMR yield was obtained. A further improved yield of 60 % was reached by reducing the temperature to 60 °C, employing 1.5 equiv. of the aryl iodide 2b and AgOAc and 50 mol % of NBE N1 (Table 1b). To further prompt the reactivity, different NBEs were investigated. The C2 amide substituted NBE N2 was

![Table 1: Optimization for meta-\(\text{C-H}\) arylation.\[24\]](attachment)

[\(^1\)H NMR analysis of the crude mixtures was determined by \(^1\)H NMR analysis of the crude mixtures using CH\(_2\)Cl\(_2\) as an internal standard. \(w/o\) = without.

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found to be the most efficient modified NBE providing the meta-arylated aniline 3b in 89 % 1H NMR yield. The C2-trifluoroethyl ester-substituted NBE N3 furnished 3b in 46 % yield while C2-trifluoroethyl amide-substituted N4 afforded 3b in 80 % yield. The critical role of the NBE electron withdrawing group was highlighted by the fact that the unsubstituted NBE N0 only gave 13 % yield (for further screening of NBEs and S,O-ligands see Supporting Information, Tables S9 and S10). Finally, the amount of NBE N2 and AgOAc could be reduced to 20 mol % and 1 equiv. respectively while maintaining the excellent yield (standard conditions). Interestingly, a reduced catalyst loading of 5 mol % (Pd(OAc)2/L1) provided only a slightly reduce yield of 78 % (Table 1c). Control experiments (Table 1c) revealed the key importance of this reagent, while only trace or no product formation observed in their absence. Excluding the above (Table 2b). As expected, the reaction of the Boc-OPh and meta-protected aniline derivatives, which are less reactive and more stable than N,N-diethyl-N,N-dimethyl-N,N-diethylaniline (N1) with NBEs examined (Table 2). Aniline derivatives bearing one or two electron withdrawing groups (i.e., 3-CO,Me-2-fluoro-, 2,3-difluoro-, 3-chloro-2-fluoro-, 3-chloro-2-methyl- and 2,3-dichloroaniline 1h–1l) were efficiently arylated (44–80 %, Table 2a), while 1-benzyl-5-chloro-1,2,3,4-tetrahydroquinoline (1m) was meta-arylated in 57 % yield (Table 2a).

Having demonstrated the generality of our methodology with meta- and ortho-meta-disubstituted anilines, we sought to explore the effect of the N-substituent on reactivity (Table 2a). While meta-fluoro N,N-dimethyl- (1n) and N,N-dimethylaniline (1o) were meta-arylated in excellent yields (80–94 %), the reaction of 3-fluoro-N-methyl-N-phenylaniline (1p) afforded the arylated product 3p in 54 % yield. Importantly, no other regioisomers from the arylation of the other phenyl group were detected, underlining the importance of the meta-substituent in facilitating the reaction. Further, 1-(3-fluoroaryl)pyrrolidine (1q) was arylated in 48 % isolated yield by increasing the temperature to 100°C and slightly modifying the concentration of the reaction.

We expanded the substrate scope by evaluating Boc-protected aniline derivatives, which are less reactive and more stable than N-alkyl secondary and tertiary anilines (see above) (Table 2b). As expected, the reaction of the Boc-protected meta-fluoro aniline 1r provided the arylated product in only 10 % yield (by 1H NMR) under standard conditions, but upon increasing the reaction temperature to 100°C and utilizing 50 mol % of modified NBE N1, an

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**Table 2:** Scope of meta- and ortho-meta-(di)substituted aromatic amines. 

<table>
<thead>
<tr>
<th>NBE</th>
<th>Substrate</th>
<th>Yield</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>L1</td>
<td>51 %</td>
<td>20 mol % AgOAc, 10 mmol L1, 100 °C</td>
</tr>
<tr>
<td>N2</td>
<td>L1</td>
<td>80 %</td>
<td>20 mol % AgOAc, 10 mmol L1, 100 °C</td>
</tr>
<tr>
<td>N3</td>
<td>L1</td>
<td>80 %</td>
<td>20 mol % AgOAc, 10 mmol L1, 100 °C</td>
</tr>
<tr>
<td>N4</td>
<td>L1</td>
<td>80 %</td>
<td>20 mol % AgOAc, 10 mmol L1, 100 °C</td>
</tr>
<tr>
<td>N0</td>
<td>L1</td>
<td>13 %</td>
<td>20 mol % AgOAc, 10 mmol L1, 100 °C</td>
</tr>
</tbody>
</table>

[a] Yield was determined by 1H NMR analysis of the crude mixtures of at least two reactions (average) using CH3Br2 as an internal standard. Isolated yields are given in the square brackets. [b] Yields without (w/o) L1 were determined by 1H NMR analysis of the crude mixture using CH3Br2 as an internal standard. [c] 100 °C. [d] 0.3 M CHCl3. [e] 2.0 equiv. AgOAc. [f] 20 mol % NBE N1. [g] Isolated with a side product.
**Table 3: Scope of ortho-substituted aromatic amines.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Product</th>
<th>Isolated Yield %</th>
</tr>
</thead>
</table>
| ortho-Constraint | meta-aryl | 48%
| Low Reactivity | Slow NBE extrusion | 41%
| Ortho-aryl | meta-aryl recovered reactivity | 56%

*For further information, see Supporting Information.*

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**Table 2: Optimization of reaction conditions.**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield %</th>
</tr>
</thead>
</table>
| 1b | 43%
| 2b | 67%
| 3b | 71%
| 4c | 58%
| 5c | 60%
| 6b | 48%

*Isolated yields are given in the square brackets.*

---

**Figure: Scope of ortho Substrates**

- **(a)** ortho-Constraint meta-aryl complex to generate the functionalized products. Interestingly, the reaction using the more stable Boc-protected 4-fluoroindoline 1s furnished the arylated product in 56 % yield, with up to 82 % yield observed when the reaction was performed at 100 °C using 20 mol % of NBE N1. Next, Boc-protected 4-methyl- and 4-methoxy-indolines 1t and 1u were meta-arylated in 59 % and 53 % yield, respectively, using 50 mol % NBE N1. Additionally, THQs 1v and 1w were arylated in synthetically useful yields. The performance of the new S,O-ligand L4 was also evaluated for substrates 1s-1w, but no remarkable increase or lowering of yields was observed under the standard conditions. Finally, we also performed the reactions without the S,O-ligand, with up to 8 % yield was observed (Table 2), demonstrating the critical role of the S,O-ligand in these transformations.

We decided to subject our catalytic system to reactivity against ortho-substituted anilines, being intrinsically challenging substrates due to the ortho-constraint (Table 3). The ortho-constraint is the necessity to have an ortho-substituent adjacent to the initial palladium insertion site to enable the extrusion of the NBE mediator from the Pd complex to generate the functionalized products. Interestingly, the group of Dong found that NBE extrusion could enable the extrusion of the NBE mediator from the Pd complex to generate the functionalized products. Interest-

etent on the benzene ring, could be meta-arylated by using our Pd/S,O-ligand catalyst in combination with bridgehead substituted NBEs. Pyrroloindoline (4f) and furoindole derivatives (4g) were efficiently meta-arylated at 80 °C using 20 mol % NBE N5. Although N-alkyl or N-benzyl unsubstituted THQs were unstable, the Boc-protected THQ 4h was successfully arylated in 60 % (H NMR yield) under the standard conditions. Further, 4-fluorinated cyclopentane 4i (56 %) and tetrahydro-9-pyridoindoline 4j (43 %) were meta-arylated in synthetically useful yields.

The applicability of the reaction to aryl halides was interrogated using the 3-methylamine 1b as a model substrate (Table 4a). A range of para-substituted methyl 2-iodobenzoates were tolerated, affording the arylated products in 77–86 % isolated yield. The reaction using the meta-arylated substituted methyl 2-iodobenzoate proceeded with 71 % yield, while other ortho-substituted aryl iodides with a coordinating functional group were also compatible, providing the desired products 7h (83 %) and 7i (72 %) in good yields.

For the aryl iodide 6j, the desired product 7ja was obtained together with ring-fused product 7jb.
also demonstrated the efficient decarboxylation of the ortho-
ester-functionalized product 3b to 8d to show that our
methodology can provide an entry point to larger aromatic
systems through meta-arylation (Table 4b).

Although high reactivity was achieved by using aryl
iodides with a coordinating group at the ortho-
position, we decided to further explore the reaction conditions
with the aim of expanding the aryl halide scope. We performed
the studies using the 3-methylaniline 1b and methyl 4-iodo-
benzoate (2a) as model substrates using 10 mol % of Pd/L1
catalyst, 20 mol % of amide NBE N2, at 60 °C. Under these
conditions, only 14 % yield of the arylated aniline 8a was
observed (Table 5), expected due to the lower reactivity of
these aryl iodides towards oxidative addition. Different S,O-
ligands were tested under the same conditions, (Supporting
Information, Table S23) to reveal that L2 (bearing a para-
OMe substituent at the phenyl group attached to the sulfur
atom) improved the yield to 25 %, while L3 (unsubstituted
phenolic) afforded 8a in 17 % yield and L4 (phenolic S,O-
ligand with two CF3) furnished the product in 30 % yield. We
tested NBEs bearing electron-withdrawing groups not
directly attached to the alkene, as we expected the palladium
complex derived from these NBEs to be more electron rich
and therefore more prone to oxidative addition. To our
delight, when using 1 equiv. of the 5,6-disubstituted NBE N7,
previously used by the group of Dong for ortho-unsubstituted
aryl iodides,17b a 46 % yield was achieved. A range of 5,6-
disubstituted NBEs were tested (Table 5), revealing NBE
N12 to be the most efficient, providing the arylated product
in 66 % yield. Finally, the yield was increased to 71 % (67 %
isolated yield) by lowering the amount of AgOAc to 1.0 equiv.
and slightly increasing the reaction concentration to 0.8 M
(Supporting Information, Tables S23–25). With the optimal
conditions in hand, the reaction with the para-nitro
phenyl iodide provided the arylated product in 52 % yield.
The reaction with the more challenging para-toluene- and
phenyl-iodide afforded the arylated products in synthetically
useful yields (41–42 %). Finally, the aryl bromide with an
ester group at the ortho-position 2e was also reactive,
providing the arylated product in 72 % yield.

To have a better understanding of the factors that
influence this transformation, we performed the reaction of

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**Table 4:** Scope of aryl halides with ortho-EWGs.[a]

<table>
<thead>
<tr>
<th>Aryl Halide</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>91% [84%]</td>
</tr>
<tr>
<td>7b</td>
<td>91% [85%]</td>
</tr>
<tr>
<td>7c</td>
<td>92% [86%]</td>
</tr>
<tr>
<td>7d</td>
<td>93% [80%]</td>
</tr>
<tr>
<td>7e</td>
<td>89% [81%]</td>
</tr>
<tr>
<td>7f</td>
<td>62% [77%]</td>
</tr>
<tr>
<td>7g</td>
<td>73% [71%]</td>
</tr>
<tr>
<td>7h</td>
<td>86% [83%]</td>
</tr>
<tr>
<td>7i</td>
<td>74% [72%]</td>
</tr>
</tbody>
</table>

[a] Yield was determined by 1H NMR analysis of the crude mixtures of at least two reactions (average) using CH2Br2 as an internal standard. Isolated yields are given in the square brackets.

**Table 5:** Optimization and scope of aryl halides.[b]

<table>
<thead>
<tr>
<th>Aryl Halide</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>71% [67%]</td>
</tr>
<tr>
<td>8b</td>
<td>59% [52%]</td>
</tr>
<tr>
<td>8c</td>
<td>47% [41%]</td>
</tr>
<tr>
<td>8d</td>
<td>49% [42%]</td>
</tr>
</tbody>
</table>

[b] The yield was determined by 1H NMR analysis of the crude mixtures using CH2Br2 as an internal standard. Isolated yields are given in the square brackets.
the unsubstituted N-dibenzylaniline 1a with methyl 4-iodo-
benzoate 2a using stoichiometric amounts of catalyst (1 equiv. of Pd(OAc)₂ and ligand L1). However, to our surprise, no desired diarylated product 3a was observed at 60 or 90°C (Table 6). Instead, we found the exclusive (90 % yield) formation of complex C1a, resulting from the para-C–H activation and subsequent migratory insertion of the NBE N₁ (entries 1–2). Interestingly, even the more reactive aryl iodide 2b provided only traces amount of the diarylated product 3a, with the major product being complex C1a (entry 3). Next, we evaluated the reactivity of the meta-
substituted aniline 1b under stoichiometric conditions with both aryl iodides 2a and 2b at 60°C (Table 6, entries 4–5). The less reactive aryl iodide 2a provided a mixture of the desired arylated product 8a alongside complex C1b, whereas the more reactive aryl iodide 2b only affording the arylated product 3b. These results indicate that next to a slow oxidative addition, the meta-substituent on the aniline may promote the second C–H activation step.

To further prove the role of the meta-substituent in the second C–H activation, as well as to have a better understanding of the role of the C2-substituent of NBE in the reaction, both complexes C1a–b and additionally their analogues with the amide NBE N₂ were synthesized by adding all reagents in equal amounts in chloroform. After 5 h at 60°C, complexes C1a–C1d were isolated in good yields (70–82 %) after purification by column chromatography (Table 7a). Similar to previous reports, the presence of four signals corresponding to the two ortho- and two meta-protons in the ¹H NMR spectra of complexes C1a and C1c indicates the coordination of the palladium center to the arene.[20,28] Although we were unable to obtain single crystals with any of the complexes C1a–C1d, we converted complex C1a to C2 by ligand exchange with 1,10-phenanthroline, and obtained a single crystal by layering heptane over C2 in DCM.[29] With the intention to obtain a more rigid structure, complex C1e using N,N-dimethylaniline, ligand L5 and amide NBE N₂, was synthesized in 43 % yield. To our delight, suitable samples for single-crystal X-ray diffraction analysis were obtained by slow evaporation from EtOAc, thereby confirming the structure of the complex.[29]

With the complexes C1a–C1d in hand, the meta-C–H activation step was investigated by performing deuterium experiments (Table 7b). When complex C1a was treated with

![Table 6: Stoichiometric reactions.](https://onlinelibrary.wiley.com/doi/10.1002/ange.202317741)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
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<th>R²</th>
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<th>Cta</th>
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<tr>
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<td>90</td>
<td>CO₂Me</td>
<td>traces (3a)</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>60</td>
<td>CO₂Me</td>
<td>n.p. (3a)</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>60</td>
<td>CO₂Me</td>
<td>traces (3a)</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>60</td>
<td>CO₂Me</td>
<td>20 (8a)</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>60</td>
<td>CO₂Me</td>
<td>60 (3b)</td>
<td>n.p.</td>
</tr>
</tbody>
</table>

[a] The yield was determined by ¹H NMR analysis of the crude mixtures using CH₃Br₂ as an internal standard. Isolated yields are given in the square brackets.


(a) Synthesis of Pd-complexes

<table>
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<td>80</td>
<td>CO₂Me</td>
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<tr>
<td>4</td>
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<td>N₂</td>
<td>43%</td>
<td></td>
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<tr>
<td>5</td>
<td>H</td>
<td>80</td>
<td>N₂</td>
<td>43%</td>
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</table>

(b) Deuterium experiments

![Image](https://onlinelibrary.wiley.com/doi/10.1002/ange.202317741)

<table>
<thead>
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<td>&lt;5</td>
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<tr>
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<td>Me</td>
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</tr>
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<td>5</td>
<td>H</td>
<td>80</td>
<td>30</td>
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(c) Catalytic activity of Pd-complexes

![Image](https://onlinelibrary.wiley.com/doi/10.1002/ange.202317741)

<table>
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<th>R²</th>
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<td>H</td>
<td>80</td>
<td>N₂</td>
<td>43%</td>
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</table>

[a] The yield was determined by ¹H NMR analysis of the crude mixtures using CH₃Br₂ as an internal standard. Isolated yields are given in the square brackets.

3 equiv. of AcOD-d$_4$ at 60°C or 80°C, less than 5% deuterium incorporation was observed, confirming the second C–H activation of the unsubstituted substrate does not occur under standard conditions. In contrast, treatment complex C1b with 3 equiv. AcOD-d$_4$ at 60°C resulted in 25% deuterium incorporation at the meta-position. Therefore, we propose that the meta-substituent — in addition to enhancing the NBE extrusion as previously demonstrated by the group of Dong [25c] — plays a vital role in entropically promoting the second C–H activation. Similarly, 20% (60°C) and 30% (80°C) deuterium incorporation was observed for complex C1c (Table S36). Consistent with our hypothesis, the palladium atom of the phenolic ligand provides slightly higher yields for Boc-protected anilines than for the unsubstituted aniline (Table 8 and Supporting Information, Table S30). The reaction using the NBE ester N1 afforded traces of diarylated product 9a, while the Cy-bridgehead substituted NBE N6 afforded at 80°C the monoarylated product 9b in 25% yield, highlighting that the bridgehead substituent also has an (probably entropic) effect on the meta-C–H activation step (entries 1 and 3).

**Table 8: Reactivity of 1a with different NBEs.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>NBE</th>
<th>Sa/b</th>
<th>Spi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N1 (-CO$_2$Me)</td>
<td>&lt;5 (9a)</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>N6 (-CO$_2$MeCy)</td>
<td>25 (9b)</td>
<td>7</td>
</tr>
</tbody>
</table>

[a] The yield was determined by $^1$H NMR analysis of the crude mixtures using CH$_3$Br$_2$ as an internal standard. [b] Monoarylated product 9b is the main product but small amounts of diarylated product 9a are observed in the $^1$H NMR crude.

**Conclusions**

In conclusion, we have developed the first general meta-selective C–H arylation of aromatic amines by Pd/S,O-ligand/NBE catalysis. By the judicious choice of the S,O-ligand and NBE mediator, more challenging substrates including ortho-substituted anilines and aryl iodides lacking an electron withdrawing group at the ortho-position are also tolerated. Preliminary mechanistic investigations suggest that the meta-substituent on the aniline substrate as well as the amide group and the bridgehead substituent in the NBE mediator have a positive effect in promoting the meta-C–H activation.

**Supporting Information**

Experimental procedures, compounds characterizations, crystallographic data and mechanistic studies. The authors have cited additional references within the Supporting Information (Ref. [31–72]).

**Acknowledgements**

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**Conflict of Interest**

The authors declare no conflict of interest.

For selected examples of para-C–H arylation reactions are reported (references 4j and 5b).

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When the aniline has an ortho-substituent, only secondary anilines are suitable substrates for the reaction. For a detailed explanation, see reference 4c.

For selected reviews on Pd/NBE cooperative catalysis, see: a) J. Wang, Y. Zhou, X. Xu, P. Liu, G. Dong, \textit{Nat. Chem.} 2018, 10, 866–872.

Similar reactivity has been previously observed on Pd/NBE catalysis (references 26 and 17b).

When the aniline has an ortho-substituent, only secondary anilines are suitable substrates for the reaction. For a detailed explanation, see reference 4c.


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[79] TURBOMOLE Version 7.7.1 (TURBOMOLE Gmbh, Karlsruhe, Germany).

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