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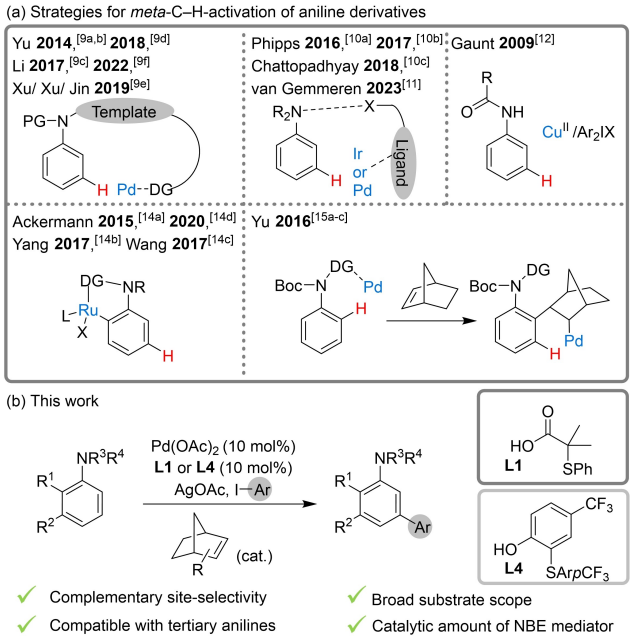
meta-C–H Arylation of Aniline Derivatives via Palladium/ S,O-Ligand/Norbornene Cooperative Catalysis

*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.[1] 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.[2] 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.[3] On the other hand, the *para*-C–H functionalization of anilines has been accomplished by exploiting the intrinsic steric and electronic reactivity of this position in non-directed approaches.[4–8] 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 aniline derivatives have been described by several authors following the pioneering work of Yu.[9] Non-covalent interactions have enabled the Ir-catalyzed *meta*-C–H borylation of anilides and quaternary anilinium salts.[10] 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.[11] The *meta*-C–H arylation of anilides combining a copper catalyst and diphenyliodonium salts was reported by the group of Gaunt.[12] 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.[13] 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.

[*] V. Sukowski, M. van Borselen, Dr. S. Mathew, Prof. Dr. B. de Bruin, Prof. Dr. M. Á. Fernández-Ibáñez
Van't Hoff Institute for Molecular Sciences
Science Park 904, 1098 XH Amsterdam (The Netherlands)
E-mail: m.a.fernandezibanez@uva.nl

where *ortho*-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*-C–H functionalization of Boc-protected anilines.[15] To date, no methodologies for the direct *meta*-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*-C–H arylation of aniline derivates, 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.

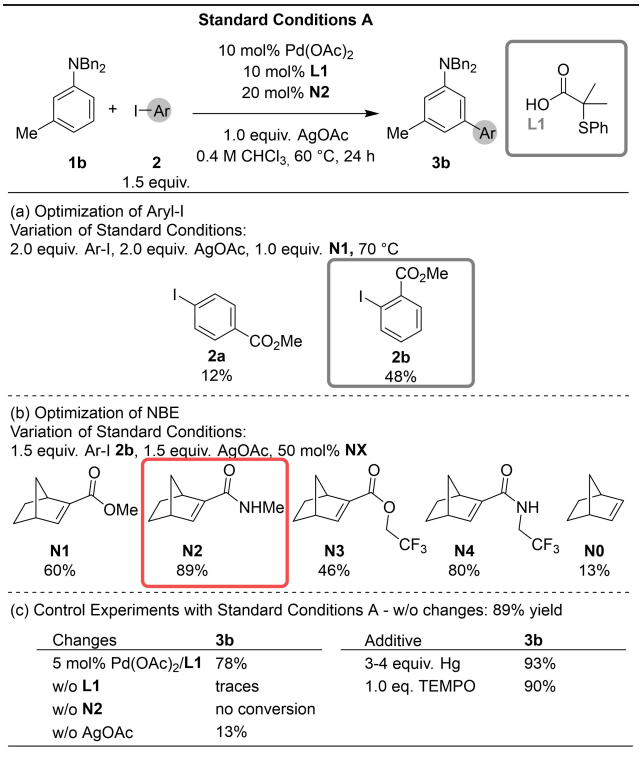
Recently, ligand-enabled non-directed C–H activation in combination with NBE mediators has emerged as a valuable tool to functionalize the less electronically favored position of arenes with high selectivity.[16–18] In this context, in 2019 a seminal work on the *meta*-C–H arylation of electron-rich alkoxyarenes was reported by the group of Yu.[16a] In this seminal publication, limitations of the catalytic system were noted, such as the lack of reactivity of anisoles 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–H functionalization reactions on a wide variety of arenes including simple arenes, thiophenes, anilines and anisoles.[4c–e,i,19] Importantly, this catalytic system allows the functionalization of aniline and anisole 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*-C–H arylation of anisole derivatives.[20] The new methodology overcomes the previously mentioned limitations (see above), allowing for example the functionalization of a wide number of anisole derivatives, including those with several electron withdrawing substituents. Therefore, taking into account that the Pd/S,O-ligand catalyst was suitable for the C–H olefination of a wide range of aromatic amines[4c] and is compatible with the norbornene mediator,[20] we hypothesized that we could develop the first *meta*-C–H arylation of underivatized anilines using simple aryl iodides as coupling partners. Herein, we report a general and efficient *meta*-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 rendering them unreactive in other Pd/NBE cooperative catalysis[17a,18,21] — are also tolerated. Preliminary mechanistic investigations provide useful insights into the role of the aniline *meta*-substituent in the substrate and the NBE mediator in the C–H activation step.

Results and Discussion

Initially, we performed the C–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 % 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*-C–H arylation.[a]



(c) Control Experiments with Standard Conditions A - w/o changes: 89% yield

Changes	3b	Additive	3b
5 mol% $Pd(OAc)_2$/**L1**	78%	3-4 equiv. Hg	93%
w/o **L1**	traces	1.0 eq. TEMPO	90%
w/o **N2**	no conversion		
w/o AgOAc	13%		

[a] Yield was determined by ^{1}H NMR analysis of the crude mixtures using CH_2Br_2 as an internal standard. w/o = without.

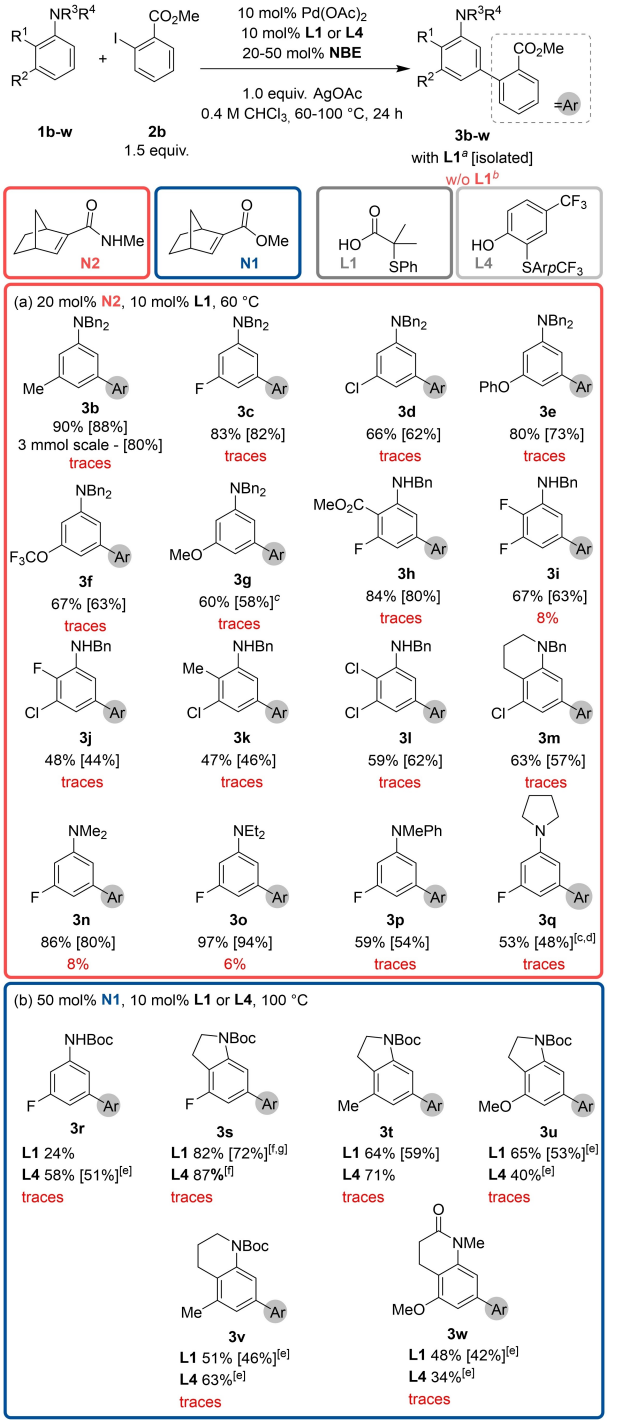
found to be the most efficient modified NBE providing the *meta*-arylated aniline **3b** in 89 % ^{1}H NMR yield. The C2-trifluoroethyl ester-substituted NBE **N3** furnished **3b** in 46 % yield while C2-trifluoroethyl amide-substituted **N4** afforded **3b** in 80 % yield. The critical role of the 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 role of the S,O-ligand **L1** and the NBE, with only trace or no product formation observed in their absence. Excluding AgOAc resulted in a reduced yield (13 %) proving the importance of this reagent.[23] Addition of TEMPO or Hg did not hamper the reactivity, indicating non-radical homogeneous catalysis.

With optimized reaction conditions in hand, a scope of different *meta*-substituted *N,N*-dibenzylanilines was examined (Table 2). Aniline derivatives bearing *meta*-Me, –F, –Cl, –OPh and $–OCF_3$ substituents provided the desired *meta*-arylated product **3b**–**3f** in good isolated yields (62–88 %) and perfect regioselectivity. Additionally, we employed model substrate **1b** to perform the reaction at a 3 mmol scale to obtain 1.0 g of product (80 % isolated yield, Table 2a). Under the standard reaction conditions (60 °C) substrate *meta*-OMe substituted **1g** afforded the arylated product **3g** in only 36 % yield, which was improved to a 58 % isolated yield upon increasing the temperature to 100 °C (Table 2a). Remarkably, *ortho*- and *meta*-disubstituted *N*-benzylanilines containing one or two electron withdrawing groups (i.e., 3-CO_2Me-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),[24] 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*-diethylaniline (**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-fluorophenyl)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 ^{1}H NMR) under standard conditions, but upon increasing the reaction temperature to 100 °C and utilizing 50 mol % of modified NBE **N1**, an

Table 2: Scope of *meta*- and *ortho*,*meta*-(di)substituted aromatic amines.[a,b]



[a] Yield was determined by ^{1}H NMR analysis of the crude mixtures of at least two reactions (average) using CH_2Br_2 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 CH_2Br_2 as an internal standard. [c] 100 °C. [d] 0.3 M $CHCl_3$. [e] 2.0 equiv. AgOAc.[f] 20 mol % NBE **N1**. [g] Isolated with a side product.

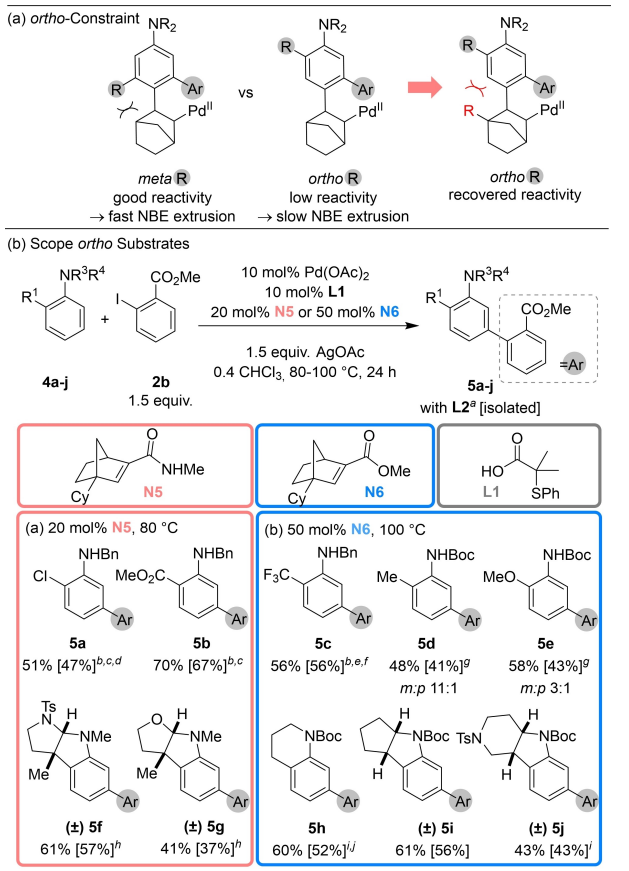
improved yield of 24 % was achieved. Further optimization of reaction conditions allowed us to obtain the *meta*-arylated product **3r** in 51 % yield with perfect regioselectivity, by using 2.0 equiv. of AgOAc and the modified S,O ligand **L4** featuring a phenolic structure (Supporting Information, Table S14). We also evaluated diverse indolines and 1,2,3,4-tetrahydroquinolines (THQs) in view of their ubiquitous occurrence in natural products and pharmaceuticals (Table 2b). The reaction of *N*-methyl or *N*-benzyl 4-fluoroindoline **1sa** and **1sb** at 60 °C provided the arylated product in 12 % and 30 %, respectively, due to the instability of the substrates under the reaction conditions (see Supporting Information for further information, Table S15). Gratifyingly, 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 3a).[21b,25] 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 also be facilitated by using bridgehead substituted NBEs by increasing the steric interaction in the palladacycle intermediate.[25c] Therefore, we performed a thorough optimization of the reaction conditions (Supporting Information, Tables S17–S20) and found that amide- (**N5**) and ester- (**N6**) Cy-bridgehead substituted NBEs were the most suitable for *ortho*-substituted anilines (Table 3b). The arylation reaction of benzyl protected 2-Cl, 2-CO_2Me and 2-CF_3 anilines **4a**–**c** using 20 mol % of **N5** or **N6** at 80 °C provided the arylated products with perfect regioselectivity in synthetically useful yields (47–67 %) In contrast, the benzyl protected 2-methylaniline was *meta*-arylated in only 29 % yield, with a significant amount of aniline decomposition observed. Therefore, we evaluated the more stable Boc-protected anilines **4d**–**e**. Like in Table 2, we found that the ester NBE is more suitable for Boc-protected anilines. The reaction of **4d** (100 °C with 50 mol % of NBE **N6**) afforded 48 % conversion (^{1}H NMR) and a *meta:para* ratio of 11:1, from which the *meta*-product was isolated in 41 % yield. The same conditions were employed for the 2-methoxyaniline **4e** attaining a 58 % ^{1}H NMR yield with a selectivity of 3:1 *meta:para*, where the *meta*-product was isolated in 43 % yield (Table 3b).

With these results in hand, we envisioned that more complex indolinines and THQs, without additional substituent 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 % (^{1}H NMR yield) under the standard conditions. Further, 2,3-indoline-fused cyclopentane **4i** (56 %) and tetrahydro-9-pyridoindoline **4j** (43 %) were *meta*-arylated in synthetically useful yields.

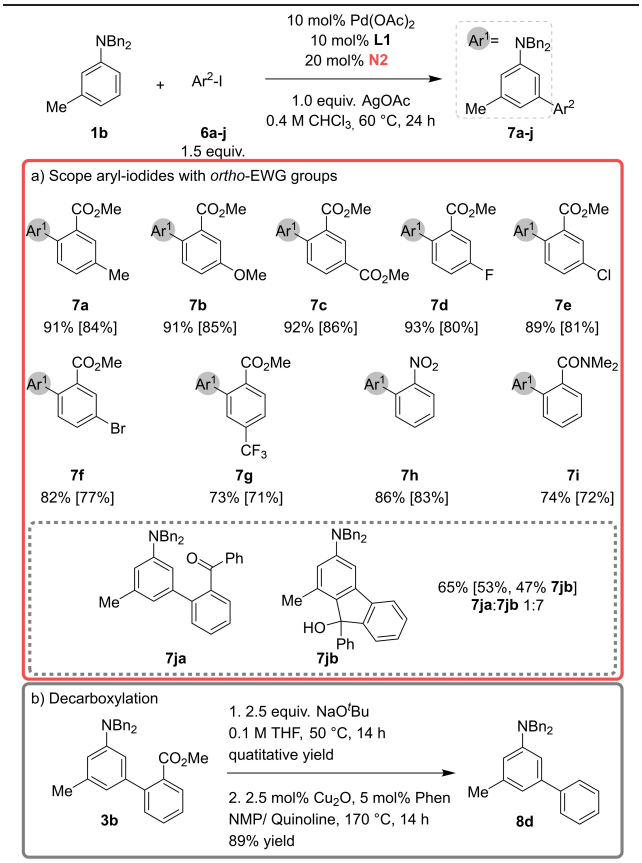
The applicability of the reaction to aryl halides was interrogated using the 3-methylaniline **1b** as a model substrate (Table 4a). A range of *para*-substituted methyl 2-iodobenzoates were tolerated, affording the arylated products in 77–86 % isolated yield. The reaction using the *meta*-CF_3 substituted 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**.[17b,21c,26,27] We

Table 3: Scope of *ortho*-substituted aromatic amines.[a]



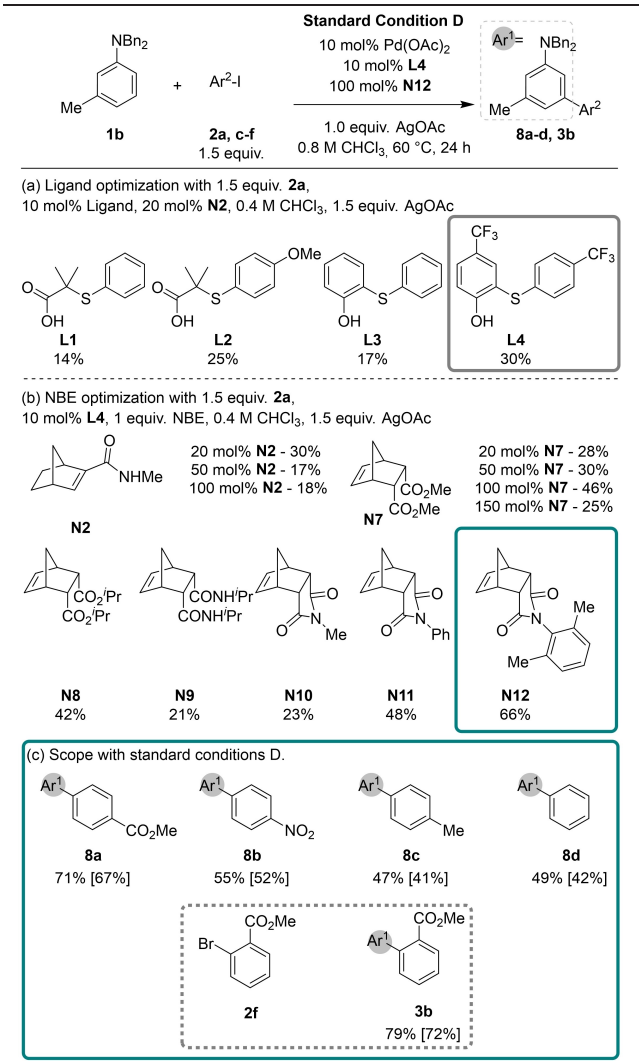
[a] Yield was determined by ^{1}H NMR analysis of the crude mixtures of at least two reactions (average) using CH_2Br_2 as an internal standard. Isolated yields are given in the square brackets. [b] 0.8 M CH_2Cl_2. [c] 1.5 equiv. aniline derivative and 1.0 equiv. Ar-I**2b**. [d] Addition of 1.0 equiv. HFIP. [e] 80 °C.[f] 20 mol % **N6**. [g] 0.8 M $CHCl_3$. [h] 1.0 equiv. AgOAc. [i] 2.0 equiv. AgOAc. [j] Isolated with a side product.

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



[a] Yield was determined by ^{1}H NMR analysis of the crude mixtures of at least two reactions (average) using CH_2Br_2 as an internal standard. Isolated yields are given in the square brackets.

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



[a] The yield was determined by ^{1}H NMR analysis of the crude mixtures using CH_2Br_2 as an internal standard. Isolated yields are given in the square brackets.

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-iodobenzoate (**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 CF_3) 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.

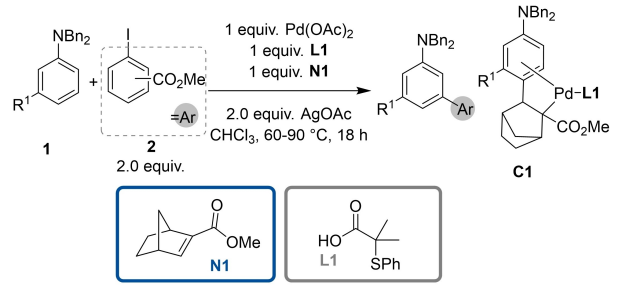
To have a better understanding of the factors that influence this transformation, we performed the reaction of

the unsubstituted *N*-dibenzylaniline **1a** with methyl 4-iodobenzoate **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 **9a**, 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 ^{1}H 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

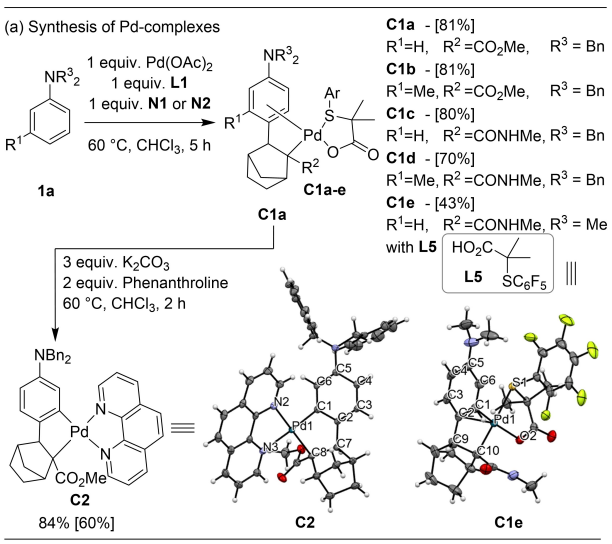
Table 6: Stoichiometric reactions.[a]

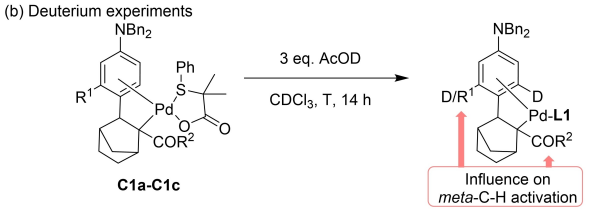


Entry	1	2	Temp [°C]	Product		C1a
1	**1a** R^1=H	**2a** *para*-CO_2Me	90	traces	(**3a**)	60
2	**1a** R^1=H	**2a** *para*-CO_2Me	60	n.P	(**3a**)	90
3	**1a** R^1=H	**2b** *ortho*-CO_2Me	60	traces	(**9a**)	82
				3b		**C1b**
4	**1b** R^1=Me	**2a** *para*-CO_2Me	60	20	(**8a**)	32
5	**1b** R^1=Me	**2b** *ortho*-CO_2Me	60	60	(**3b**)	n.P.

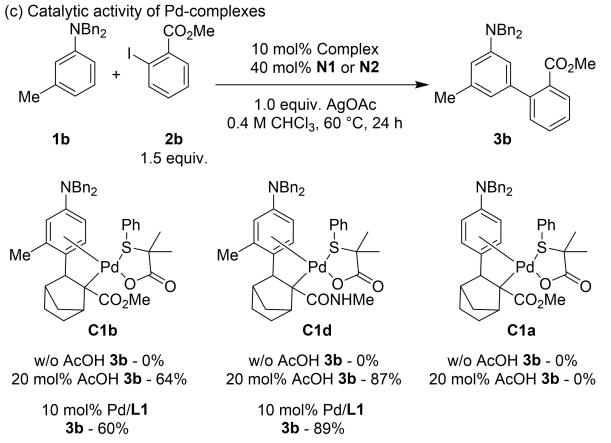
[a] The yield was determined by ^{1}H NMR analysis of the crude mixtures using CH_2Br_2 as an internal standard.

Table 7: Synthesis and reactivity of Pd-complexes.[a]





Entry	C1		Temp [°C]	D%
1	**C1a** R^1=H	**N1** (-CO_2Me)	60	<5
2	**C1a** R^1=H	**N1** (-CO_2Me)	80	<5
3	**C1b** R^1=Me	**N1** (-CO_2Me)	60	~25
4	**C1c** R^1=H	**N2** (-CONHMe)	60	~20
5	**C1c** R^1=H	**N2** (-CONHMe)	80	~30



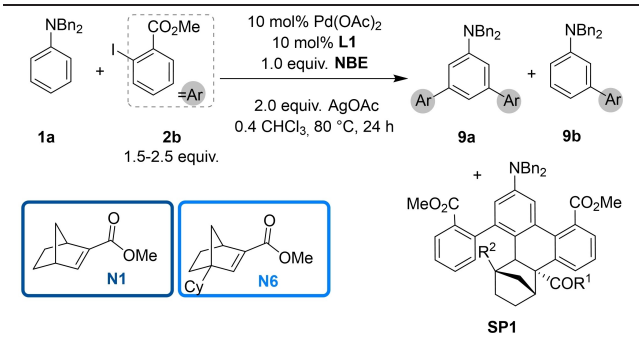
[a] The yield was determined by ^{1}H NMR analysis of the crude mixtures using CH_2Br_2 as an internal standard. Isolated yields are given in the square brackets.

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 7b), revealing that the NBE amide substituent promotes the *meta*-C–H activation which is consistent with previous reports.[21c,30] Given that C2-amide NBEs **N2** or **N5** are more effective than ester NBEs for tertiary or secondary anilines, and for Boc-protected anilines, ester NBEs **N1** or **N6** outperform amide NBEs (Tables 2 and 3), we propose that when the *meta*-hydrogen is less acidic, as in tertiary or secondary anilines, and thus less prone to activation by a CMD mechanism, the use of amide NBE is advantageous as it facilitates the *meta*-C–H activation step. Additionally, KIE measurements suggest that the *meta*-C–H activation is the rate-determining step (see Supporting Information, Table S33). Further, the catalytic activity of complexes **C1a**, **C1b** and **C1d** was investigated in the model reaction with *N,N*-dibenzy-3-methylaniline (**1b**) using 10 mol % of the complex and 40 mol % of the corresponding NBE **N1** or **N2** (Table 7c). Surprisingly no product formation was observed, but the addition of 20 mol % of AcOH (formed during the catalytic reaction) afforded similar yields for complexes **C1b** and **C1c** compared to the catalytic reaction, indicating that these complexes are catalytically active.

In our investigation, we observed that the phenolic S,O-ligand provided slightly higher yields for Boc-protected anilines (Table 2) and when using less reactive aryl iodides (Table 5). In both cases, the oxidative addition is less facile as the palladium complex derived from Boc-protected anilines should be less electron rich than that coming from tertiary anilines and aryl iodides without an *ortho*-coordinating group are less susceptible to oxidative addition. Thus, we speculate that the phenolic S,O-ligand facilitates the oxidative addition step by forming a more electron rich palladacycle. To confirm this hypothesis, we calculated by DFT the charge of the palladium center in the complexes with either a phenolic (**L4**) or carboxylic acid S,O-ligand (**L1**) before the oxidative addition step (after the second C–H activation step) (Supporting Information, Table S36). Consistent with our hypothesis, the palladium atom of the phenolic ligand complex is more electron rich and therefore more likely to promote the oxidative addition.

Finally, the effect of various NBEs in the catalytic reaction with the unsubstituted aniline **1a** was explored (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.[a]



Entry	NBE	9a/b	SP1
1	**N1** (-CO_2Me)	<5 (**9a**)	6
2	**N6** (-CO_2Me/Cy)	25 (**9b**)[b]	7

[a] The yield was determined by ^{1}H NMR analysis of the crude mixtures using CH_2Br_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]).

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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: Anilines · Arylation · C – H Activation · Ligand Design · Palladium

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