Ortho Arylation of N-Aryl Amides and the Construction of Diagonal Tetraaryldiamines and N-Doped Picenes via BBr_3-Derived Dibromoboracycles

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KEYWORDS #Arylation #BBr_3 #C-H activation #Palladium #Suzuki–Miyaura

ABSTRACT: The synthesis of biaryl amides, which are prevalent motifs in bioactive molecules, often necessitates lengthy and inefficient procedures. To address these limitations, catalytic C-H activation protocols have emerged, enabling the direct ortho-arylation of aryl amides. However, these protocols often suffer from issues such as lack of selectivity, reliance on stoichiometric oxidants, and the requirement for excess reagents and harsh reaction conditions. To overcome these challenges, we present a novel and highly selective protocol for the ortho-arylation of N-aryl amides and ureas. The high selectivity originates from the directed installation of BBr_3 to form a boracycle, which then undergoes cross-coupling with an aryl halide. Our method offers significant advantages, including mild reaction conditions, excellent site-specificity, and scalability. The protocol demonstrates broad compatibility with a diverse range of readily accessible functionalized anilides and aryl iodides, as evidenced by 55 successful examples yielding products in the 30–95% range. Furthermore, our methodology surpasses conventional approaches by facilitating the one-pot selective diagonal diarylation of dianilides. This capability unlocks the construction of previously unattainable diagonal aryl systems, which serve as valuable precursors for the synthesis of diagonal tetraaryldiamines and N-doped picenes, two crucial compound classes in materials science.

Introduction

Biaryl motifs play a central role in the field of chemistry, finding extensive utility across natural products, materials, pharmaceuticals, and agrochemicals.[1] The synthesis of these ubiquitous motifs often relies on transition-metal-catalyzed C-H activation reactions.[1d, 2] One particular significant dimension of this research centers on the site-selective *ortho* arylation of *N*-aryl amides. This area has captivated substantial attention in the scientific community due to the significance of 2-aminobiaryls, a key product of this arylation, as recurrent structural motifs in various pharmaceutical and agrochemical molecules (Figure 1A).[1b, 1c, 3] In the pursuit of synthesizing these *ortho*-arylated *N*-aryl amides, a diverse range of metal catalysts, including Cu, Ru, Rh, and Pd, has been employed (Figure 1B).[4] Despite the promising results, these methods suffer from critical drawbacks, including the requirement for stoichiometric amounts of oxidants,[4a, 4c-4g, 4l] excess of electrophilic arenes,[4a-4g, 4j] harsh reaction conditions,[4d, 4e, 4f, 4g, 4h] challenges in controlling selectivity,[4b, 4c, 4g, 4h, 4j] a limited scope of applicable substrates,[4b-4d, 4h, 4j] and the use of expensive metal catalysts.[4a, 4e-4g] Furthermore, an even greater limitation with these methods is that they are inherently unsuitable for the selective diagonal diarylation of dianilides (Figure 1B). Dianilides are of strategic value as they have been identified as a suitable starting point for the synthesis of *N*-doped picenes and diagonal tetraaryldiamines (DTADA) (Figure 1C). Both classes of compounds hold significant importance in material chemistry where they found usages as organic field-effect transistors (OFETs), organic photovoltaics (OPVs), and organic light-emitting diodes (OLEDs).[5]

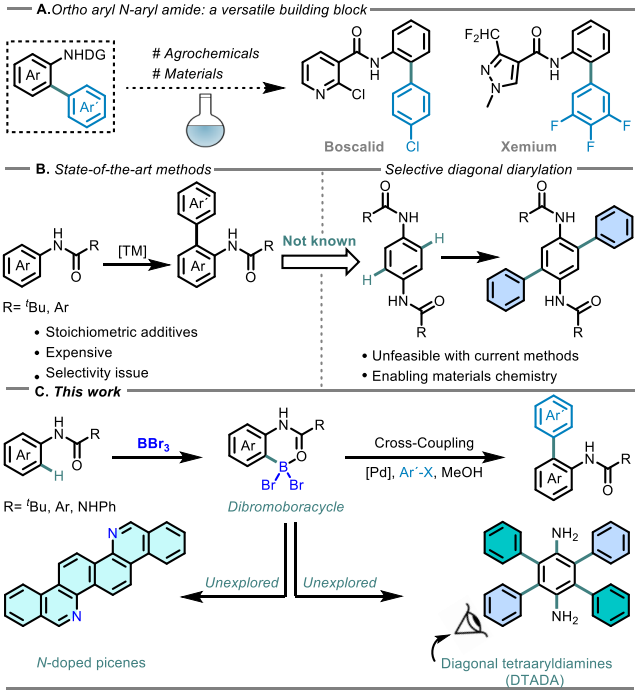

Figure 1. A) Importance of *ortho* functionalized *N*-aryl amides. B) State-of-the-art methods for *ortho* arylation of *N*-aryl amides

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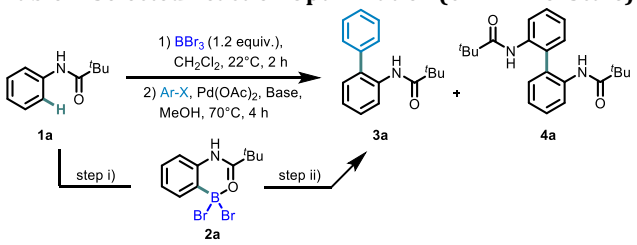
and challenges in selective diagonal diarylation. C) This work: Ortho arylation of *N*-aryl amides and the construction of diagonal tetraaryldiamines and *N*-doped picenes.

Given the limitations and drawbacks associated with the current *ortho* C-H activation methods for *N*-aryl amides, there is a strong motivation to develop new protocols that can effectively address these issues. Recently, Boron tribromide (BBr_3) has been successfully employed in metal-free approaches for incorporating boron pinacol esters (Bpin),[6] hydroxy group,[6c] and halogens[7b] at the *ortho* position of anilides. The common denominator to achieving this type of chemistry is the formation of the di-bromo-boracycle (Figure 1 C), which can be introduced through carbonyl as a directing group.[8]

We envisioned that the site-selectively formed di-bromo-boracycle (Figure 1C) could serve as an ideal boron coupling partner in the traditional Suzuki-Miyaura cross-coupling (SMC) reaction for installing aromatic groups *ortho* to the anilide. This strategic utilization allows us to streamline the synthetic process by minimizing the need for a separate step to convert the di-bromo-boracycle into BPin.[6] In this work our focus centers on the Suzuki–Miyaura C(sp^2)-C(sp^2) cross-coupling reaction of di-bromo-boracycles and will address challenging issues such as chemoselectivity, substrate scope limitations, and the stoichiometric usage of oxidant and additives encountered with contemporary methods. Furthermore, we take this work one step further by demonstrating its utility in the diagonal arylation of dianilides, a reaction that forms the basis for the step-economical synthesis of a variety of *N*-doped PAHs. This is exemplified by the unprecedented synthesis of *N*-doped picene and DTADAs.

Table 1. Selected Reaction Optimization (0.22 mmol Scale)[a]

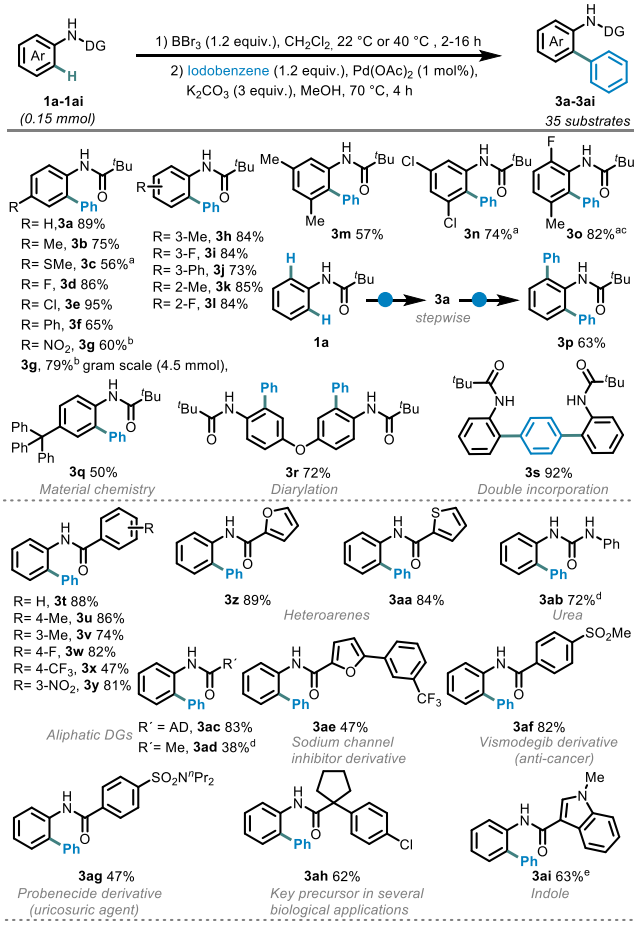


Entry	Catalyst (mol%)	Base (equiv.)	Yield[e] (3a)	Yield[e] (4a)
1[a]	$Pd(OAc)_2$ (1)	K_2CO_3 (3)	89%[f]	3%[f]
2[b]	$Pd(OAc)_2$ (1)	K_2CO_3 (3)	84%[h]	6%[f]
3	$Pd(OAc)_2$ (5)	K_2CO_3 (3)	88%	6%
4	$PdCl_2(dppf)$ (1)	K_2CO_3 (3)	86%	3%
5	$PdCl_2(PPh_3)_2$ (1)	K_2CO_3 (3)	85%	6%
6	$Pd(PPh_3)_4$ (1)	K_2CO_3 (3)	46%	5%
7	----	K_2CO_3 (3)	0%	0%
8	$Pd(OAc)_2$ (1)	Na_2CO_3 (3)	85%	4%
9	$Pd(OAc)_2$ (1)	Cs_2CO_3 (3)	69%	5%
10	$Pd(OAc)_2$ (1)	----	0%	0%
11[c]	$Pd(OAc)_2$ (1)	K_2CO_3 (3)	45%	3%
12[d]	$Pd(OAc)_2$ (1)	K_2CO_3 (3)	15%	2%

[a]Reaction conditions: Step i) **1a** (0.15 mmol), BBr_3 (0.18 mmol), in 0.5 mL anhydrous CH_2Cl_2 at 22 ^{0}C, 2 h; Step ii) iodobenzene (0.18 mmol), potassium carbonate (K_2CO_3, 0.45 mmol), $Pd(OAc)_2$ (1 mol%), in 1.5 mL MeOH at 22 ^{0}C to 70 ^{0}C for 4 h; [b]Bromobenzene instead of iodobenzene; [c]Ethanol as solvent; [d]Step 2 at RT; [e]GC yields, *o*-xylene as an internal standard; [f]Isolated yields; entries 3-12 Iodobenzene was used.

RESULTS AND DISCUSSION

Having identified optimal conditions for introducing boron to the *ortho* position of anilides through the reaction of anilides with BBr_3 in our previous work,[7b] the primary focus of this study was to determine reaction conditions facilitating the utilization of boracycle **2a** as a coupling partner in the SMC reaction. Thus, our optimization commenced with screening of reaction conditions for the SMC reaction (Table 1). As it turns out 1.2 equiv. of iodobenzene (entry 1, Table 1) in the presence of 1 mol% $Pd(OAc)_2$ and potassium carbonate (K_2CO_3) gave the *ortho* arylated product **3a** in excellent 89% yield, alongside with a minor amount of the self-coupling product **4a** (3% yield). Bromobenzene also works as an electrophile in the reaction providing **3a** in 84% yield along with **4a** in 6% yield. Due to the lesser amount of self-coupling product with iodobenzene, we decided to further explore the SMC reaction using iodobenzene.



Scheme 1. Reaction Scope. *N*-aryl amides: **3a**-**3s** step 1 at 22 ^{0}C, 2 h; [a]step 1 at 40 ^{0}C for 16 h. [b]step 1 at 22 ^{0}C, 24 h. [c]step 2 for 12 h. entry **3t**-**3ai** step 1 at 40 ^{0}C. [d]step 1 at 60 ^{0}C for 24 h. [e]step 2 for 6 h.

Next, the catalyst was also investigated and it turns out that higher loading of $Pd(OAc)_2$ (5 mol%, entry 3, Table 1) did not improve the yield nor the selectivity of the reaction. Consequently, we proceeded with the 1 mol% catalyst loading for further investigation. Additionally, a screening of various palladium catalysts demonstrated that palladium (II) catalysts performs better than palladium (0) (entries 1, 4, 5

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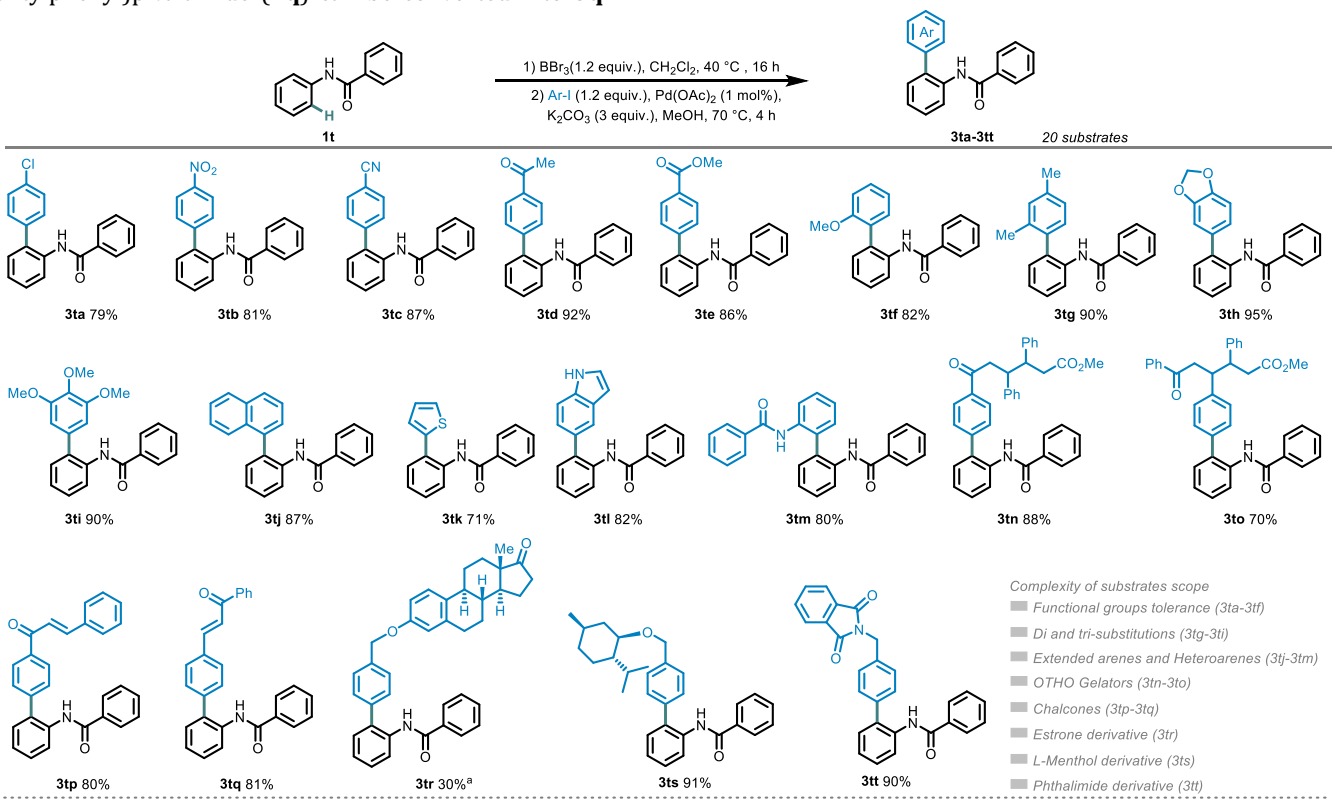
vs entry 6, Table 1). In the absence of a catalyst, desired product formation was not observed (entry 7, Table 1), showing that the reaction does not proceed via an uncatalyzed *ipso* addition. Screening of bases revealed that K_2CO_3 gave the best outcome compared to Na_2CO_3 and Cs_2CO_3 (entry 1 vs. entry 8 and 9) and in the absence of a base the reaction does not work (entry 10, Table 1), confirming the crucial role of the base in this transformation. Moreover, a change of solvent from methanol to ethanol gave a sluggish reaction and provided the desired product in 45% yield (entry 11, Table 1). Furthermore, conducting the reaction at room temperature also resulted in a sluggish reaction and a lower yield (15% yield, entry 12, Table 1).

Having found our optimal reaction conditions (table 1, entry 1) the substrate scope was explored. First, the protocol was tested on a diverse set of *para*-substituted *N*-phenyl pivalamides, leading to the corresponding *ortho*-arylated products **3a-3g** in good to excellent yields (56%-95%, Scheme 1). For example, *para*-substituted fluoro- and chloro-pivaloyl anilides are well tolerated by the reaction and the corresponding products **3d** and **3e** can be isolated in 86% and 95% yield, respectively. Additionally, electron donating substituents also performes well and *p*-NO_2 containing product **3g** can be isolated in 79% yield in a gram-scale experiment. Furthermore, substitution at the *ortho*- and *meta*-position with substituents such as methyl, phenyl, and fluoro groups are also accommodated by the reaction providing the arylated congeners in good to excellent yields (**3h-3l**, 73%-85%, Scheme 1). The arylation can also be performed with disubstituted substrates. For example, 3,5-dichloranilide can be smoothly converted into **3n** 74% yield. Also, di-arylation can be performed on substrate **1a** providing **3p** in 63% yield (Scheme 1). *N*-(4-tritylphenyl)pivalamide (**1q**) can be converted into **3q** in 50% yield. It is worth highlighting that diarylation can be readily accomplished under similar conditions on substrate containing two pivalamide groups such as **1r** in a 72% yield (**3r**, Scheme 1). By employing 1,4-diiodobenzene the arylation occurs twice and product **3s** can be isolated in excellent 92% yield (Scheme 1).

Next, the scope was investigated for a series of benzamide directing groups. As it turns out the reaction is compatible with substituents such as methyl, fluoro, -CF_3, and -NO_2 in the *para* and *meta* position on the benzamide aryl ring and the corresponding products can be isolated in good to excellent yields (**3t-3y**, 47%-88%, Scheme 1). Hetero-aromatic substrates such as furan and thiophene exhibited both high reactivity in the reaction, providing the desired products **3z** and **3aa**, in excellent 89% and 84% yield, respectively (Scheme 1). It is noteworthy to mention that a substrate containing urea performed well in the reaction, yielding the arylated product **3ab** in a significant 72% yield, despite the potential for urea to coordinate with palladium and potentially quench the reaction (See Table 2). Next, alternative acyl groups were tested in the reaction. For example, adamantyl is accommodated by the reaction, and the desired product **3ac** can be isolated in an 83% yield. The acetyl group also worked; however, the yield is lower, and **3ad** is isolated in a 38% yield (Scheme 1). Due to the prevalence of the anilide functional group in several biologically active compounds, we seized the opportunity to examine substrates with known pharmaceutical properties, featuring varying levels of molecular complexity. Evidently, these substrates were well tolerated, and the reaction produced the desired arylated products in good to excellent yields (**3ae-3ai**, 47%-82%, Scheme 1). For instance, a vismodegib derivative can be arylated to yield **3af** in an 82% yield.



Scheme 2. Reaction scope, Aryl iodides: [a]1.3 equiv. of aryl iodide

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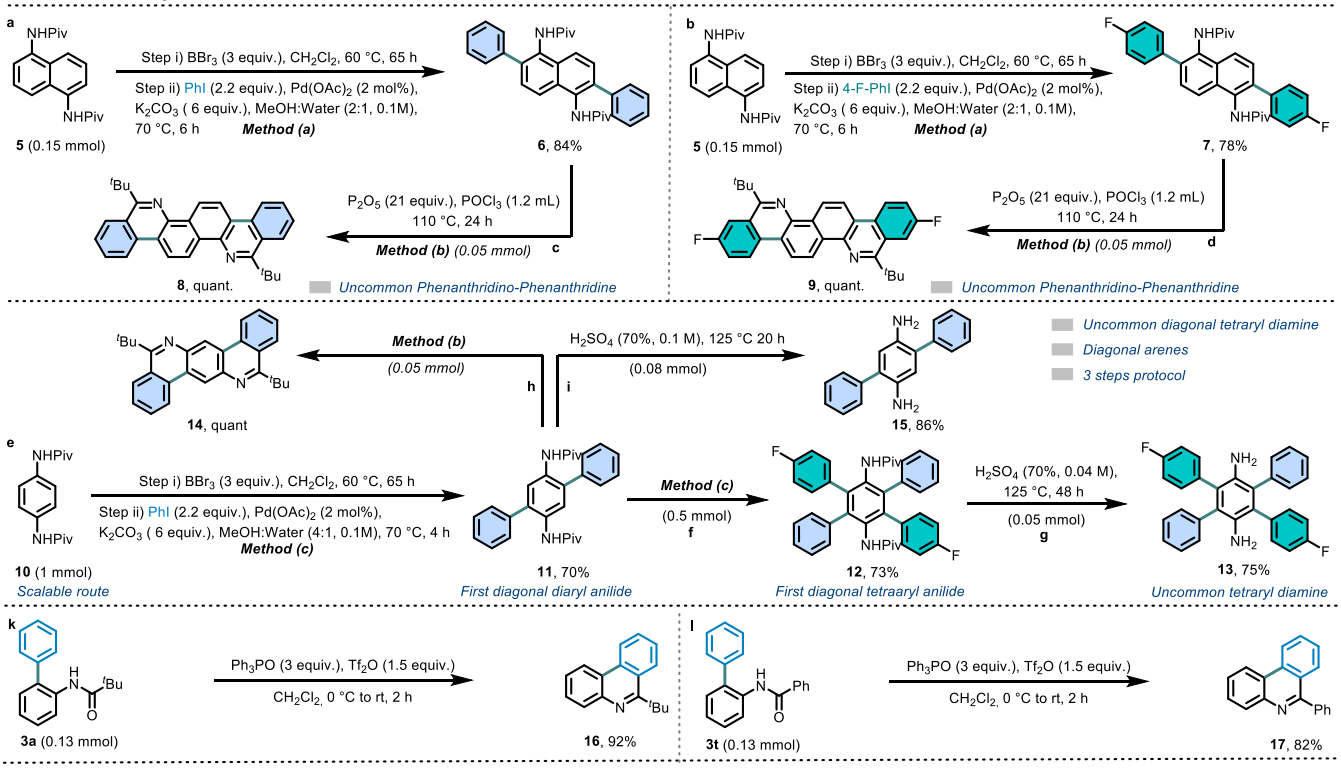
After successfully exploring the substrate scope involving the aniline moiety and a range of different directing groups, we proceeded to investigate the reactivity of various aryl iodides in combination with benzanilide (**1t**) as a starting material. Evidently, the reaction exhibited high functional group tolerance, as a diverse set of aryl iodides could be accommodated in the reaction. For example, aryl iodides with -chloro, -cyano, -nitro, -ketone, and -ester functional groups were duly accommodated at the *para* position, yielding the desired products in excellent yields (**3ta-3te**, 79%-92%, Scheme 2). Additionally, the electron-donating methoxy group at the *ortho* position, as well as substrates with disubstitution, trisubstitution, and naphthyl group, exhibited excellent reactivity in the reaction (**3tf-3tj**, 82%-95%, Scheme 2). Furthermore, heteroarene-containing substrates, including thiophene, unprotected indole, and amide, were well tolerated in the reaction, yielding the desired products in very good yields (**3tk-3tm**, 71%-82%, Scheme 2). For example, 5-iodo-1H-indole readily couples with **1t** to give the indole derivative **3tl** in 82% yield. Our exploration then progressed to oxotriphenylhexanoate (OTHO) molecules, which are low molecular weight gelators capable of self-assembling into three-dimensional (3D) networks within the solvent.[9a] To our delight, even though these substrates were complex and prone to cyclize under BBr_3 conditions,[9bc] we did not observe such reactivity under our optimized conditions and provided excellent yields of products **3tn** and **3to** isolated in 88% and 70%, respectively (Scheme 2). This highlights the strength of our protocol in efficiently designing and synthesizing complex molecules. Additionally, we investigated coupling with iodide containing chalcone substrates and found that they were also well tolerated in the reaction without any undesired Heck-type side reactions catalyzed by palladium in excellent yields (**3tp** and **3tq**, 80% and 81%, Scheme 2). Lastly, we ventured into more complex substrates possessing pharmaceutical relevance, including estrone, L-menthol and phthalimide derivatives. We were pleased to find that these challenging substrates were also well tolerated in the reaction, yielding the desired products in yields ranging from low to excellent (**3tr-3tt**, 30%-91%, Scheme 2).

Within the dynamic domain of advanced materials, polycyclic aromatic hydrocarbons (PAHs) distinguish themselves through their multifaceted utility. From organic field-effect transistors (OFETs) to catalysis, PAHs have become integral to diverse fields.[5] As *N*,*N*'-(1,4-phenylene)diamides have been identified as suitable starting points for the synthesis of a number of substances in materials chemistry for the aforementioned applications, we set out to test whether our method could be useful for the diagonal functionalization of *N*,*N*'-(1,4-phenylene)diamides. As it turns out, subjecting naphthalene-derived dianilide **5** to our developed two-step reaction conditions rendered diphenyl-functionalized dianilide **6** in 84% yield (Scheme 3 a). It is naturally important to point out that the phenyl group can be altered, subjecting **5** to 4-fluoroiodobenzene gives the fluorinated diagonally arylated compound **7** in 78% yield (Scheme 3b). Having established a robust synthesis for the diagonally diarylated dianilide **6** and **7**. We were able to show case there utility as starting materials in the quantitative synthesis of *N*-doped picene-derivatives **8** and **9** (Scheme 3c and 3d) demonstrating the versatility and effectiveness of our optimized protocol in accessing complex molecular architectures.



Scheme 3. Applications= a) and b) Synthesis of diagonal diaryl systems. c) and d) Synthesis of phenanthridino-phenanthridine derivatives. e) Synthesis of diagonal diphenyldianilides. f) Synthesis of diagonal tetraphenyldianilides (DTPDA); Condition: step ii) 4-F-PhI (3 equiv.), MeOH:Water (3:2), time-18 h. g) and i) Pivaloyl deprotection. h) Synthesis of isoquinolino-phenanthridine derivative. k) and l) Synthesis of phenanthridine derivatives.

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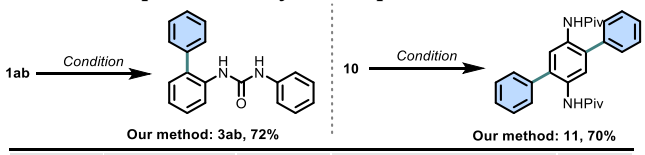
Having developed the first synthesis of di-arylated dianilides, we were interested to see if the method would be applicable for the synthesis of DTADA (Scheme 3e-g). We initiated the synthesis by installing two aryl units in diagonal fashion on **10**, resulting in the desired product **11** in a 70% yield. Next, **11** was utilized for a second diagonal di-arylation, yielding the desired diagonal tetraaryl dipivalamide, **12**, that was isolated in notable 73% yield (Scheme 3f). Synthesis of tetraaryl substituted dianilide is particularly noteworthy as their synthesis is unprecedented. The diagonal tetraaryl dipivalamide **12** can be hydrolyzed to the aniline using sulfuric acid to afford the desired DTADA **13** in 75% yield (scheme 3g). Additionally, **11** can be used for the synthesis of extended heteroaromatic systems. For example, treating **11** with P_2O_5 and $POCl_3$ yielded *N*-doped tetraphene **14** in quantitative yield.[10] Furthermore, the deprotection of the corresponding amide **11** led to the formation of diagonal diaryl-dianiline system **15** that could be isolated in 86% yield. Additionally, in the presence of Ph_3PO and Tf_2O, **3a** and **3t** could be converted into phenanthridine derivatives **16** and **17** in 92% and 82% yield, respectively.

Next, to evaluate the effectiveness of our protocol compared to other reported methodologies for directed C-H arylations, we subjected urea derivative **1ab** to various reaction conditions commonly used in such processes (entries 1-4, Table 2). Our investigation revealed that only one protocol led to the formation of the desired product **3ab**, albeit with a low yield (entry 2, Table 2). Subsequently, we extended the application of our protocol to the diagonal diarylation of substrate **10** under similar conditions (entries 5-8, table 2). Interestingly, the only reaction conditions capable of producing the desired product **11** involved a ruthenium-catalyzed process, resulting in a 7% isolated yield of the product, along with several unidentified side products (entry 6, Table 2). Emphasizing the effectiveness of our protocol for the synthesis of complex substrates and highlights the distinct reactivity patterns accessible through the *ortho*-borylation strategy.

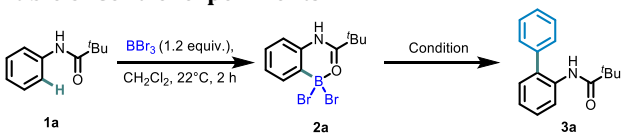
Table 2. Comparison study with reported methods



Entry	Condition	Yield (3ab)	Entry	Condition	Yield (11)
1	Rh (ref. 4f)	0%	5	Rh (ref. 4f)	0%
2	Ru (ref. 4g)	19%	6	Ru (ref. 4g)	7%
3	Pd (ref. 4h)	0%	7	Pd (ref. 4h)	0%
4	Pd (ref. 4l)	0%	8	Pd (ref. 4l)	0%

To gain further insights into the mechanism of the reaction, control experiments showed that all components of the reaction protocol such as catalyst, base, and methanol are required for optimal performance (Table 3, entry 1 vs entries 2-3 and supporting information Table 1). To assess the reactivity of complex (**2a**) and the influence of methanol on the reaction, experiments were carried out in various solvents, as detailed in Table 3 (entry 4) and SI Table 1 (entries 1-4). Surprisingly, none of the solvents proved suitable for this transformation, suggesting methanol playing a pivotal role in this process. Nevertheless, the reaction can be executed in acetonitrile with as little as 4 equivalents of methanol under otherwise similar reaction conditions, yielding the product in 82% yield (entries 5 vs entry 4, Table 3). This experiment suggests that the reaction probably progresses through ligand exchange on boron in the presence of methanol.[11]

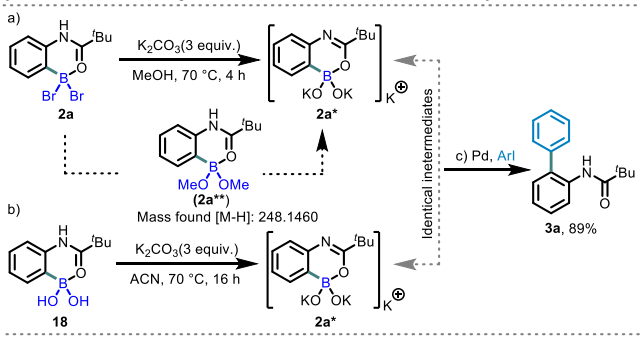
Table 3: Control experiments



Entry	deviation	Yield
1	None[a]	**3a**, 89%[b]
2	No base	**3a**, 0%[c]
3	No BBr_3	**3a**, 0%[c]
4	Step ii) CH_3CN instead of methanol, 20 h	**3a**, 0%[c]
5	CH_3CN and 4 equiv. of methanol, 20 h	**3a**, 82%[c]
6	Step ii) Only K_2CO_3, methanol, 70 ^{0}C for 4 h	**2a***[d]
7	**2c**, $Pd(OAc)_2$, PhI, ACN, 70 ^{0}C, 4 h	**3a**, 89%[b]

[a]Reaction conditions: Step i) **1a** (0.15 mmol), BBr_3 (0.18 mmol), in 0.5 mL anhydrous CH_2Cl_2 at 22 ^{0}C, 2 h; Step ii) Iodobenzene (0.18 mmol), potassium carbonate (K_2CO_3, 0.45 mmol), $Pd(OAc)_2$ (1 mol%), in 1.5 mL MeOH at 22 ^{0}C to 70 ^{0}C for 4 h. [b]Isolated yield. [c]GC yield, *o*-xylene as an internal standard. [d]Confirmed by NMR analysis. See the supporting information table 1 and section 7 for further details.

Furthermore, stirring the reaction without palladium and iodobenzene a new compound is formed as judged by the NMR of the crude reaction mixture (entry 6, Table 3, Scheme 4a). Initially we thought that it might be the boronic dimer or trimer that have formed however the cross-reaction control experiment revealed that there is no dimer or trimer formation in the reaction (Scheme 4a-b vs SI section 7.3). These results indicate that an anionic form of the boronic acid (**2a***) is likely generated in the reaction mixture via the dimethoxy intermediate (**2a****) (Scheme 4a). Subjecting **2a*** to the reaction gave **3a** in 89% yield providing strong evidence for its involvement in the reaction mechanism (Scheme 4c, entry 7 table 3 and SI section 7.4).



Scheme 4. a) Reaction of dibromo intermediate (2a) under basic condition. b) Reaction of boronic acid (18) under basic condition. c) Ortho arylation of intermediate (2a*).

To substantiate the control experiment and elucidate the formation of an intermediate **2a***, we conducted NMR studies, as depicted in Figure 2. A comparative analysis of the

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crude ^{1}H NMR spectra of dibromoboracycle (**2a**) and the reaction mixture (Scheme 4a-b) revealed distinct pattern differences for the two reactions. The observed shift differences in the spectra, particularly between **2a*** and both **2a** and **18**, suggests the formation of a previously unidentified intermediate formed in the reaction. (Figure 2). Furthermore, ^{11}B NMR validated that the intermediates contain boron and that the boron shift correlates well with what is expected for **2a*** (SI section 7.1.2).

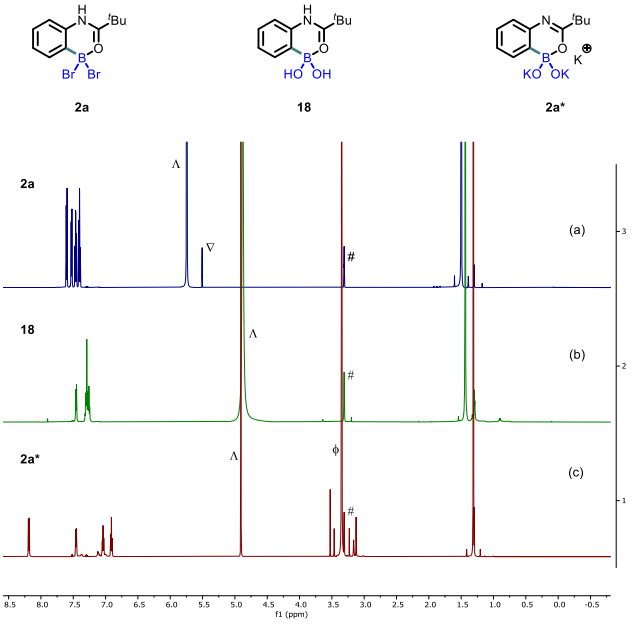
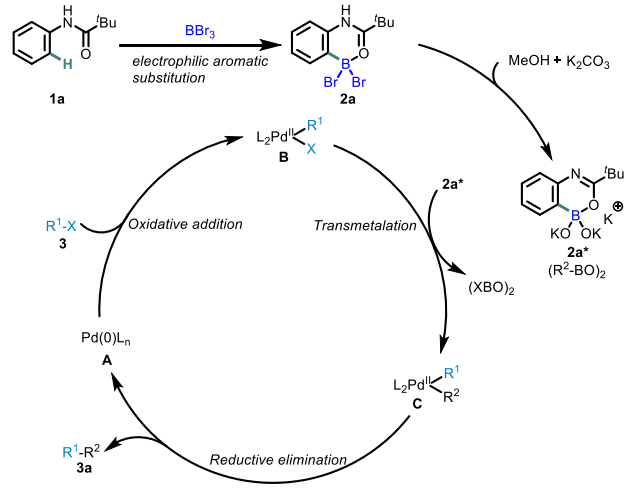


Figure 2: NMR studies: (a) Di-bromo-boracycle (2a). (b) Boronic acid (18). (c) Intermediate (2a*). NMRs were recorded in $MeOD_4$. (ϕ=residual methanol, Λ= Water, ∇= CH_2Cl_2, #= CD_3OD) For more detail refer S.I. section 7.

Based on control experiments, we propose a mechanism that initiates with carbonyl-directed borylation of **1a**, leading to the formation of the dibromo boracycle (**2a**) (scheme 5.) Subsequent base-promoted ligand exchange transforms the dibromo boracycle into its dimethoxy counterpart (**2a****)[11] (Scheme 4a) which further reacts to form **2a*** under basic condition. Compound **2a*** is more susceptible to transmetalation than its bromo counterpart **2a** as evident by the absence of product formation observed in reactions conducted without the presence of alcohol or water (entry 4 in table 3, entries 1-4 in SI table 1).



Scheme 5: Proposed mechanism

The catalytic cycle commences with the oxidative addition of the aryl halide R^1-X to palladium(0) (**A**), yielding intermediate **B**. Subsequently, intermediate **B** undergoes transmetalation with boron complex **2a***, leading to the formation of intermediate **C**. The final step in the catalytic cycle entails the reductive elimination of intermediate **C**, yielding the desired cross-coupling product (**3a**).

In conclusion, our research has successfully introduced a new and highly efficient di-bromo-boracycle as a readily accessible boron unit for the SMC reaction. By harnessing the unique properties of this di-bromo-boracycle, we have contributed to the advancement of the SMC reaction, opening up new avenues for the synthesis of valuable organic compounds. The developed method offers simplicity and mild reaction conditions with minimal catalyst loading, making it an attractive and practical choice for carbon-carbon bond formation. Notably, our approach enables the synthesis of first diagonal tetraaryl dianilides and a verity of N-doped picenes, an achievement not attainable with previously reported methods. Our work not only sheds light on the C(sp^2)-C(sp^2) cross-coupling reaction of newly derived boron reagents in SMC but also paves the way for future explorations in cross-coupling reactions. The strategic use of these boracycles as coupling partners may offer an innovative approach to accessing diverse and challenging molecular structures,[7] contributing to the advancement of modern organic synthesis.

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Notes

The authors declare no competing financial interest.

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