Ortho Arylation of N-Aryl Amides and the Construction of Diagonal Tetraaryl Anilides via BBr_3-Derived Dibromoboracycles

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ABSTRACT: In this study, we present a first comprehensive palladium-catalyzed Suzuki–Miyaura C(sp^2)-C(sp^2) cross-coupling reaction, employing newly derived di-bromo-boracycles as pivotal reagents for the synthesis of *ortho* arylated *N*-aryl amides. Our research hinges on the utilization of di-bromo-boracycles, which act as temporary reservoirs of boron, facilitating subsequent transformations in cross-coupling reaction. The di-bromo-boracycle offers a unique opportunity for regioselective carbon-carbon bond formation to the *ortho* position of *N*-aryl amides. This mild, site-specific, and scalable protocol is compatible with a wide array of easily accessible functionalized anilides and aryl iodides, as demonstrated by 55 examples, yielding products in the range of 30%-95%. Furthermore, the methodology transcends conventional practices, enabling the construction of previously unattainable diagonal aryl systems, highlighting the exceptional potential of our approach for accessing intricate molecular architectures.

Introduction

Bi(hetero)aryl 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.(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-amino-biaryls, a key product of this arylation, as recurrent structural motifs in various pharmaceutical and agrochemical molecules (Figure 1A).(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-4e, 4i) excess of electrophilic arenes,(4a-4e, 4h) harsh reaction conditions, (4b, 4d, 4f) challenges in controlling selectivity,(4e, 4f, 4h) a limited scope of applicable substrates, (4b, 4f, 4h) and the use of expensive metal catalysts. (4a, 4c-4e)

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),(5) hydroxy group,(5c) and halogens(6b) 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.(7)

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. 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.(5) 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. In addition, we are also able to show that the method can be used for the one-pot synthesis of diagonal arene systems (Figure 1C).

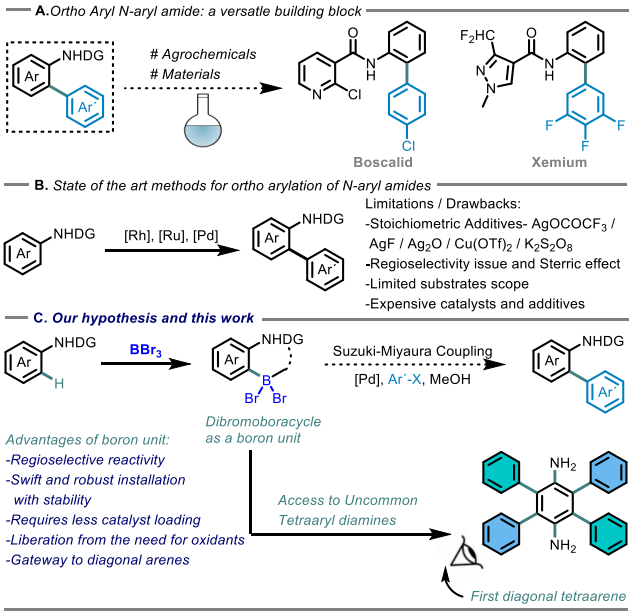
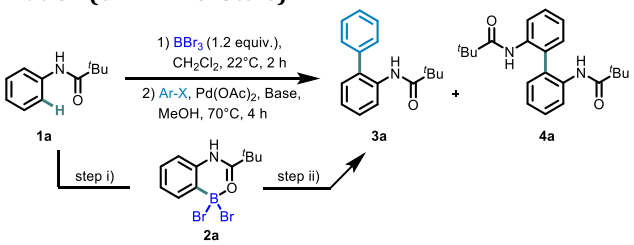


Figure 1. A) Importance of *ortho* halogenated Aryl amides. B) State-of-the-art methods for *ortho* arylation of *N*-aryl amides. C) Our hypothesis and work for the synthesis of *ortho*-arylated *N*-aryl amides and synthesis of diagonal tetraaryl anilines.

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



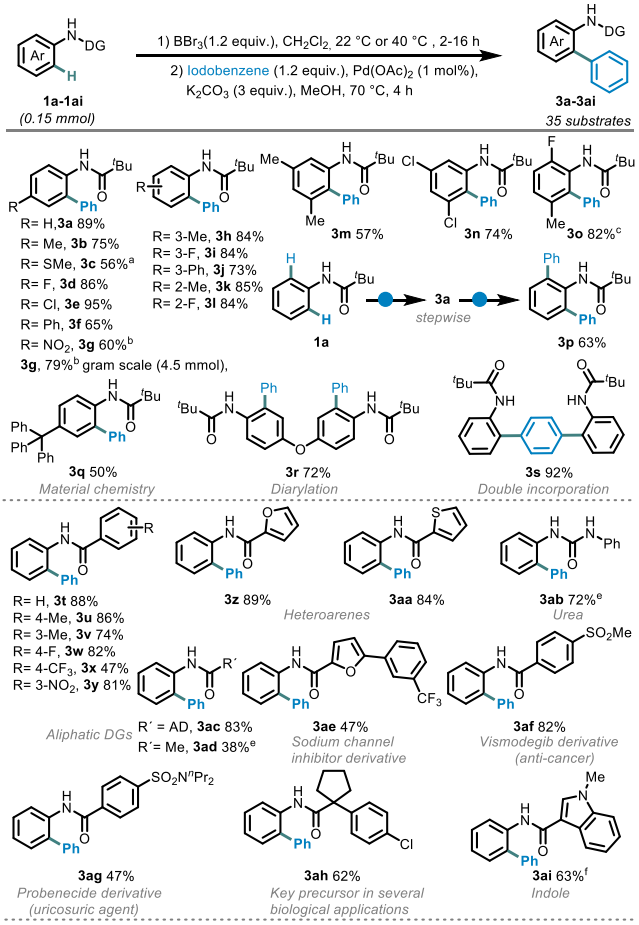
Entry	Catalyst (mol%)	Base (equiv.)	Yield[e] (3a)	Yield[e] (4a)
1[a]	$Pd(OAc)_2$ (1)	K_2CO_3 (3)	89%[f]	3%[f]
2[b]	$Pd(OAc)_2$ (1)	K_2CO_3 (3)	84%[f]	6%[f]
3	$Pd(OAc)_2$ (5)	K_2CO_3 (3)	88%	6%
4	$PdCl_2(dppf)$ (1)	K_2CO_3 (3)	86%	3%
5	$PdCl_2(PPh_3)_2$ (1)	K_2CO_3 (3)	85%	6%
6	$Pd(PPh_3)_4$ (1)	K_2CO_3 (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,[6b] 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. 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 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.



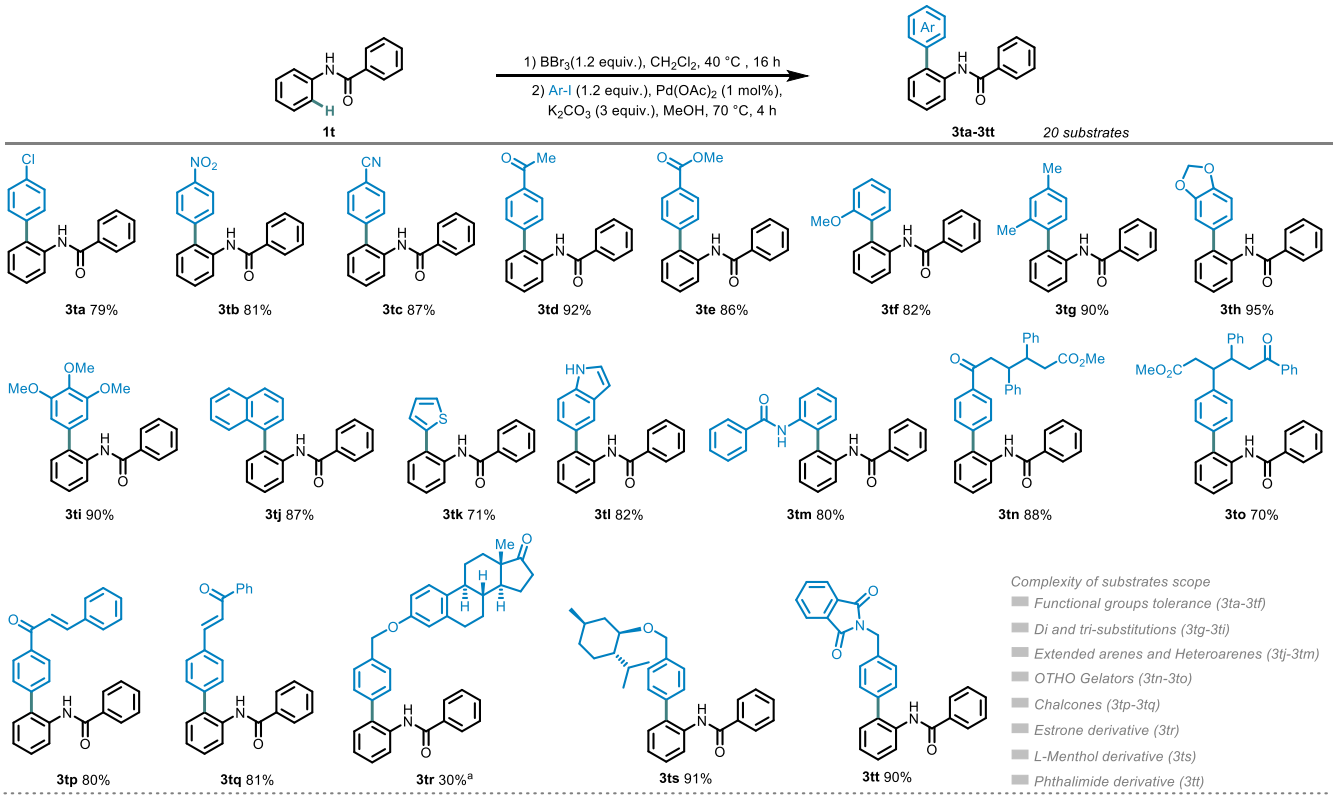
Scheme 1. Reaction Scope. *N*-aryl amides: **3a**-**3s** step 1 at 22 ^{0}C, 2 h; [a]step 1 at 40 ^{0}C for 16 h. [b]step 1 at 22 ^{0}C, 24 h. [c]step 2 for 12 h. [d]step 1 at 40 ^{0}C, 24 h, step 2 for 24 h. entry **3t**-**3ai** step 1 at 40 ^{0}C. [e]step 1 at 60 ^{0}C for 24 h. [f]step 2 for 6 h.

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 the 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. 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 **3ad** in an 82% yield.

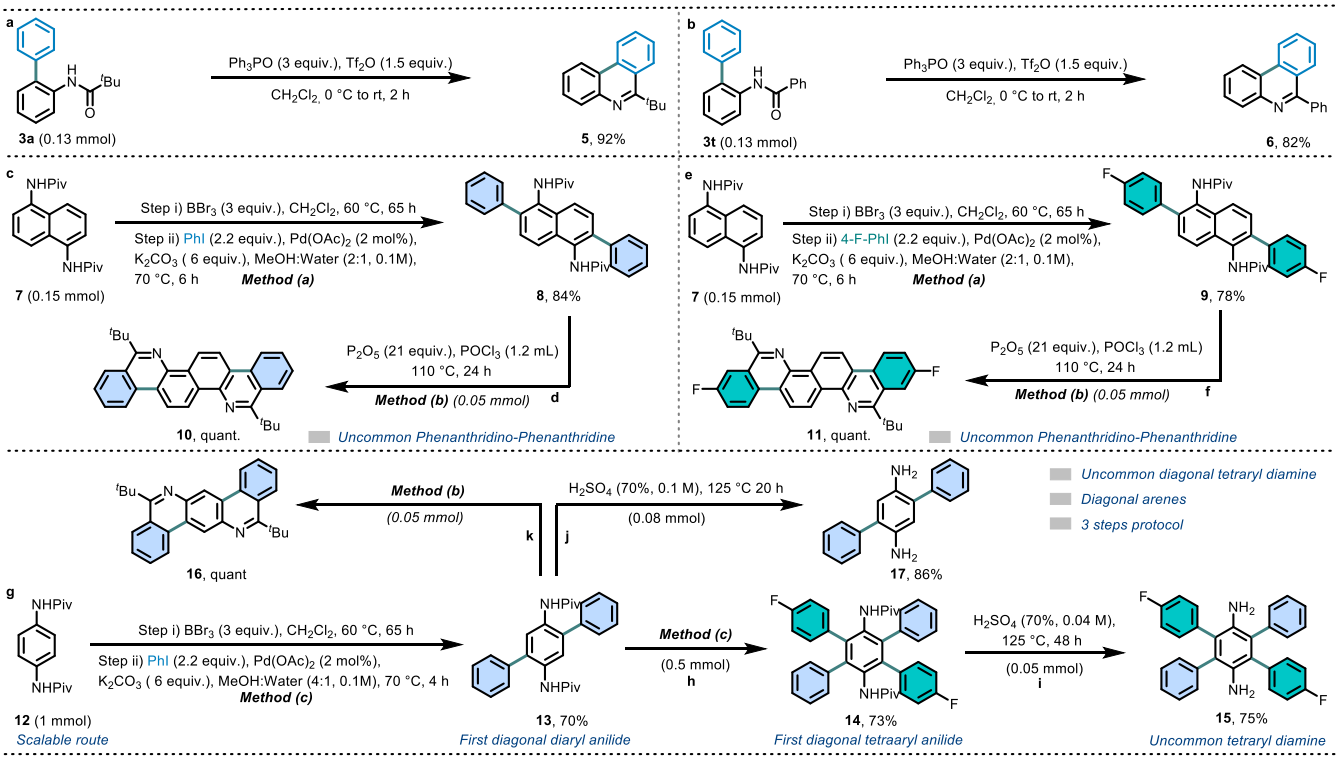


Scheme 2. Reaction scope, Aryl iodides: [a]1.3 equiv. of aryl iodide

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. Next, our exploration extended to substrates with gel properties. To our delight, even though these substrates were complex and prone to cyclize under BBr_3 conditions,[8] we did not observe such reactivity under our optimized conditions and provided excellent yields (**3tn** and **3to**, 88% and 70%, 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).

To further illustrate the synthetic value of *ortho* arylation, a number of post-transformations were performed (Scheme 3a and b). For example, in the presence of Ph_3PO and Tf_2O, **3a** and **3t** could be converted into phenanthridine derivatives **5** and **6** in 92% and 82% yield, respectively. Next, we were interested to see if our methodology could be used for the one-pot synthesis of diagonally arylated anilides, such as naphthalene substrate **7**. As it turns out, the reaction works exceptionally well, and the

desired di-aryl products **8** and **9** were smoothly obtained in 84% and 78% yield, respectively (Scheme 3c and 3e). Intriguingly, the diagonally substituted products **8** and **9** underwent further transformation into unprecedented phenanthridino-phenanthridine systems with quantitative yields (**10**-**11**, Scheme 3d and 3f). This additional demonstration further solidifies the versatility and effectiveness of our optimized protocol in accessing diverse molecular architectures.



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

Having developed the first synthesis of di-arylated dianilides, we were interested to see if the method would be applicable for the synthesis of tetra-aryl substituted anilides (Scheme 3g-h). We initiated the synthesis by installing two aryl units in diagonal fashion on **12**, resulting in the desired product 1**3** in a 70% yield. Next, **13** was utilized for a second diagonal di-arylation, yielding the desired diagonal tetraaryl pivalamide, **14**, that was isolated in notable 73% yield (Scheme 3h). Synthesis of tetraaryl substituted anilides is particularly noteworthy as their synthesis is unprecedented. The diagonal tetraaryl pivalamide **14** can be hydrolyzed to the aniline using sulfuric acid to afford the desired tetraaryl dianiline **15** in 75% yield (scheme 3i). Additionally, **13** can be used for the synthesis of extended heteroaromatic systems. For example, treating **13** with P_2O_5 and $POCl_3$ yielded **16** in quantitative yield. Furthermore, the deprotection of the corresponding amide **13** led to the formation of diagonal diaryl-diamine system **17** in a 86% yield.

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 anilides, 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, contributing to the advancement of modern organic synthesis.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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