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Aromaticity-Dependent Regioselectivity in Pd(II)-Catalyzed C−H Direct Arylation of Aryl Ureas

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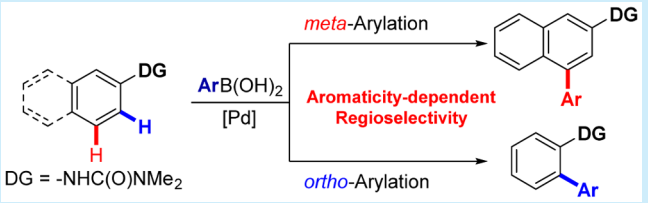
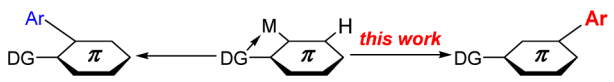
Supporting Information

ABSTRACT: Palladium-catalyzed C−H direct arylation generally occurs on the *ortho*-position of directing groups. By comparing *meta*-arylated products of 2-naphthyl urea to *ortho*-arylated products of phenyl urea, the *ortho*- and *meta*-regioselectivity of aryl ureas were found to depend on the aromaticity of the corresponding aryl substituents. Thus, aromaticity is a new factor which can affect the regioselectivity in C−H direct arylation. The finding was further confirmed by regioselective direct arylation of indole and pyrrole derivatives.



Direct C−H functionalization is one of the most powerful and atom-economical methods for the construction of C−C bonds.[1] A serious problem in this field is the control of regioselectivity when multiple C−H bonds exist in one molecule. Based on the Directed *ortho* Metalation theory, transition metal catalyzed *ortho* C−H bond direct functionalization could be realized regioselectively via the C−M bond formed *in situ* (M = transition metal). In recent years, chemists have begun developing efficient methods for achieving remote C−H bond activation.[2] For example, Yu et al. reported a covalent template strategy for remote C−H activation and norbornene as a transient mediator for *meta*-C−H activation.[2a,b] Gaunt et al. reported copper(II) catalyzed *meta*-arylation of aromatics using diaryliodonium salts as coupling partners.[2c] However, only very few studies on direct arylation of C−H bonds adjacent to *in situ* generated C−M bonds have been reported (Scheme 1).[3] Such a strategy not only can realize

Scheme 1. Direct Arylation of C−H Bond Adjacent to the C−M Bond



remote C−H bond activation but also can supply possibilities for new chemical transformations. Very recently, our group reported the palladium-catalyzed *meta*-direct arylation of *β*-naphthyl carbamate via an *ortho*-metalation/*meta*-direct arylation pathway.[4] However, direct arylation of phenyl carbamates under the same conditions proved unsuccessful, which made the nature of the regiochemical outcome puzzling. To give a clear interpretation of this unique regioselectivity, we report herein the results of the direct arylation of aryl urea derivatives. The degree of aromaticity of the aryl groups was revealed as an unexpected factor that affects the regioselectivity of C−H bond direct arylation.

At the beginning of this work, the reaction of 2-naphthyl urea **1a** with *o*-tolylboronic acid **2a** was performed under our previously reported conditions (entry 1 in Table 1). Under these conditions, 2-naphthyl urea **1a** decomposed completely and no arylated products were generated. We thus turned our attention to identifying suitable oxidative conditions for this coupling reaction. In entry 2, when $K_2S_2O_8$ was used as the oxidant in a mixture of toluene and acetic acid,[5] the monoarylated product was generated in 55% crude yield (as estimated by NMR), despite the presence of byproducts which were difficult to remove. With benzoquinone as the oxidant, the corresponding monoarylated product was not detected (entry 3). By changing the shoichiometry of the oxidant to 3.0 equiv of $PhCO_3Bu$-*t*, the estimated yield of monoarylated product was identified as 76%, with complete decomposition of the remaining starting material **1a** (entry 4). Although the use of a combination of 2.0 equiv of $PhCO_3Bu$-*t* with 1.0 equiv of $Cu(OAc)_2{\cdot}H_2O$ gave the monoarylated product in a relatively low yield (63%), starting material **1a** was recoverd, thus providing the possibility for further improvement (entry 5). In entry 6, the estimated yield from NMR data could be slightly improved to 69% when the loading of coupling partner **2a** was raised to 3 equiv. The reaction was found to be strongly affected by the acidity of the solvent. In entry 7, the reaction proceeded very poorly in toluene, giving the monoarylated product in only 39% NMR yield. In contrast, we were delighted to see the reaction proceeding smoothly in HOAc, with a 79% yield in the arylated product. With an additional 1.0 equiv of $TsOH{\cdot}H_2O$, the yield could be further improved to 85%, with

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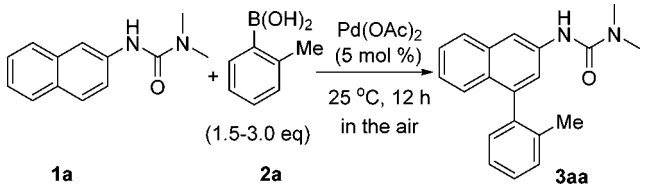
Table 1. Optimization of the Reaction Conditions for C−H Bond Direct Arylation



1a 2a 3aa

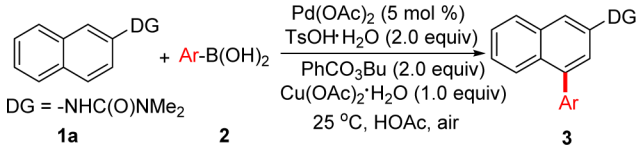
entry	oxidant (equiv)	additive (equiv)	solvent	yield[a] (%)
1	$K_2S_2O_8$ (6.0)	AgOAc (0.05)	TFA/HOAc = 2/1	N.D.[b]
2	$K_2S_2O_8$ (3.0)	TsOH·H_2O (1.0)	PhMe/HOAc = 1/1	55
3	BQ (5.0)	TsOH·H_2O (1.0)	PhMe/HOAc = 1/1	N.D.[b]
4	$PhCO_3Bu$ (3.0)	TsOH·H_2O (1.0)	PhMe/HOAc = 1/1	76
5	$PhCO_3Bu$ (2.0) $Cu(OAc)_2·H_2O$ (1.0)	TsOH·H_2O (1.0)	PhMe/HOAc = 1/1	63
6[c]	$PhCO_3Bu$ (2.0) $Cu(OAc)_2·H_2O$ (1.0)	TsOH·H_2O (1.0)	PhMe/HOAc = 1/1	69
7[c]	$PhCO_3Bu$ (2.0) $Cu(OAc)_2·H_2O$ (1.0)	TsOH·H_2O (1.0)	PhMe	39
8[c]	$PhCO_3Bu$ (2.0) $Cu(OAc)_2·H_2O$ (1.0)	TsOH·H_2O (1.0)	HOAc	79
9[c]	$PhCO_3Bu$ (2.0) $Cu(OAc)_2·H_2O$ (1.0)	TsOH·H_2O (2.0)	HOAc	85

[a]Yields were calculated according to ^{1}H NMR using 4-methoxyphenol as internal standard. [b]N.D. = not detected. [c]3.0 equiv of **2a** were used.

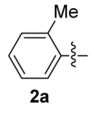
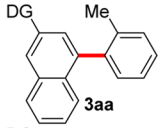
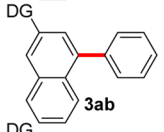
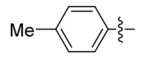
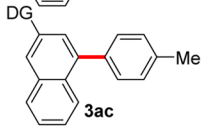
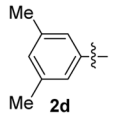
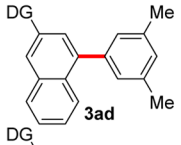
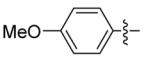
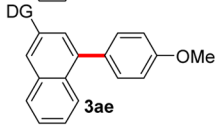
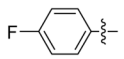
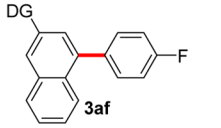
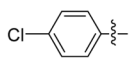
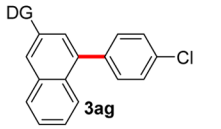
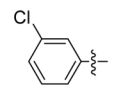
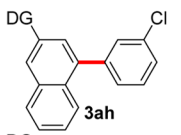
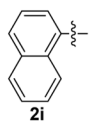
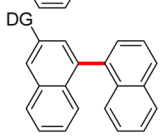
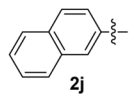
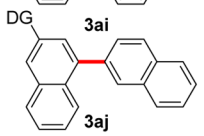
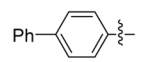
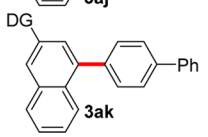
complete consumption of **1a**. Therefore, the reaction was optimally performed using 5 mol % $Pd(OAc)_2$ as a catalyst precursor, 2 equiv of $PhCO_3Bu$-*t* and 1 equiv of $Cu(OAc)_2·H_2O$ as oxidants, and 2 equiv of TsOH·H_2O as an additive at 25 °C in HOAc under an air atmosphere.

Under these optimized conditions, we examined the scope of aryl boronic acids and identified the structure of monoarylated 2-naphthyl urea (Table 2). In entry 1, the isolated yield of **3aa** was 78%. Phenyl boronic acid provided the monoarylated product **3ab** in 64% isolated yield (entry 2). By removing the *N*,*N*-dimethyl carbamic group, the resulting compound could be confidently assigned as the *meta*-phenylated 2-naphthyl amine (see Supporting Information (SI)).[6] Phenyl boronic acid bearing a methyl group on the *para*- or *meta*-position of the phenyl ring could be transformed into the corresponding *meta*-arylated products **3ac** and **3ad** in 66% and 64% yields, respectively (entry 3 and 4). Electron-rich *p*-methoxyphenyl boronic acid could give the *meta*-arylated product **3ae** in 63% isolated yield (entry 5). Phenyl boronic acids bearing electron-withdrawing substituents such as *p*-F, *p*-Cl, and *m*-Cl groups provided the *meta*-arylated products **3af**, **3ag**, and **3ah** in 60%, 52%, and 53% yields, respectively (entries 6, 7, and 8). We also tested the reactivity of polyaromatic boronic acids. Both *α*- and *β*-naphthyl boronic acids could react smoothly with **1a** to

Table 2. Scope Of Aryl Boronic Acids In Direct *meta*-Arylation of 1a



1a 2 3

entry	Ar-B(OH)2	products	yield[a] (%)
1	 2a	 3aa	78
2	 2b	 3ab	64
3	 2c	 3ac	66
4	 2d	 3ad	64
5	 2e	 3ae	63
6	 2f	 3af	60
7	 2g	 3ag	52
8	 2h	 3ah	53
9	 2i	 3ai	70
10	 2j	 3aj	55
11[b]	 2k	 3ak	78

[a]Isolated yields. [b]1.5 equiv of **1a** were used.

generate *meta*-arylated products **3ai** and **3aj** in moderate to good yields (entries 9, 10). 4-Biphenylboronic acid **2k** could also be successfully introduced on the *meta*-position of **1a**, giving **3ak** in 78% yield (entry 11). To further confirm the

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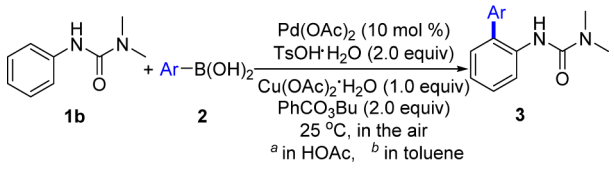
regioselectivity, X-ray diffraction of compound **3ah** was performed, and its connectivity was verified (see SI).

Next, direct arylation of phenyl ureas was investigated. As shown in Scheme 2, under the same optimized conditions as

Scheme 2. Direct Arylation of Phenyl Urea with Arylboronic Acids under Optimized Conditions



[a] in HOAc, [b] in toluene

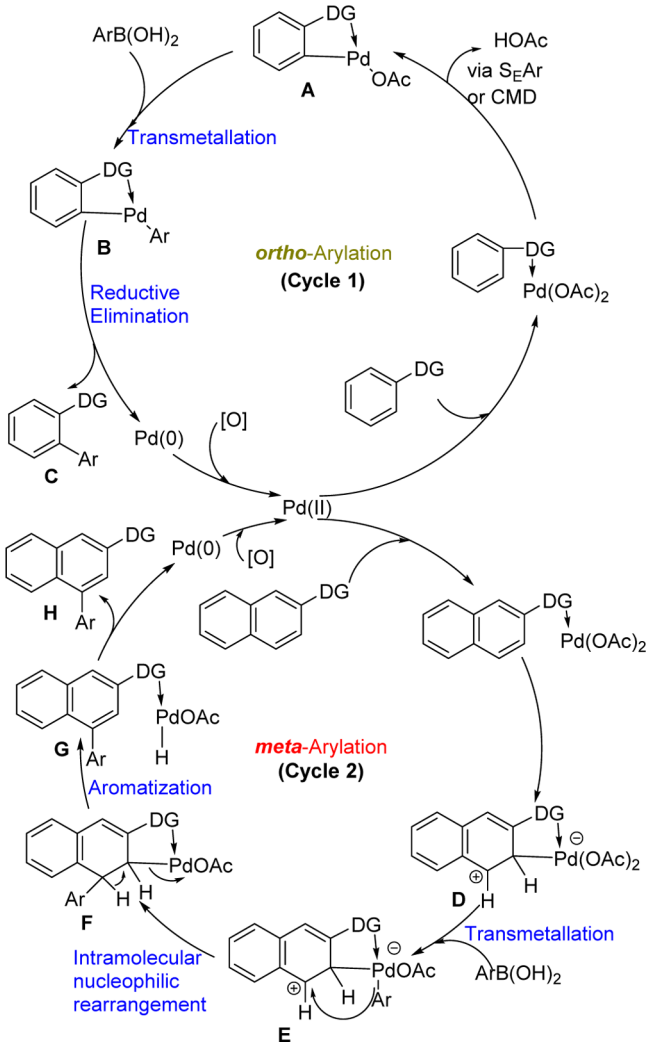
3bb, Ar = Ph	yield = 76%[a]
3bc, Ar = *p*-Me-Ph	yield = 25%[a], 57%[b]
3be, Ar = *p*-MeO-Ph	yield = 22%[a], 62%[b]
3bf, Ar = *p*-F-Ph	yield = 80%[a]
3bg, Ar = *p*-CF_3-Ph	yield = 60%[a]
3bm, Ar = *m,m*-di-CF_3-Ph	yield = 64%[a]
3bn, Ar = *m*-MeO-Ph	yield = 11%[a], 52%[b]

described above, phenylboronic acid and its electron-rich and -poor derivatives gave exclusively *ortho*-arylated products. Although the electron-rich arylboronic acids gave *ortho*-arylated products in lower yields (**3bc**, **3be**, and **3bn**), no *meta*- or *para*-arylated products were formed. Changing the solvent to toluene, the yields were effectively improved. The regioselectivity in this reaction is consistent with that in Lipshutz and coworkers' work[7] and unambiguously demonstrated that directed *ortho*-metalation could occur in this catalytic system.

According to the different regioselectivity of 2-naphthyl urea and phenyl urea, we conclude that the difference in nucleophilicity and aromaticity of the aryl groups lead to different reaction pathways. A proposed mechanism is depicted in Scheme 3. After coordination of the palladium catalyst to the directing group, electrophilic attack of the palladium catalyst to the *ortho*-position of the urea substituent occurs, generating the corresponding C−Pd bond. In this step, *ortho*-C−H bond cleavage may occur via S_EAr, concerted metalation/deprotonation (CMD) or other mechanisms, generating intermediate **A** in **Cycle 1**. Nevertheless, dearomatization of aryl groups can alternatively proceed, giving a carbocationic species **D** in **Cycle 2**. The competition between *ortho* C−H bond cleavage and dearomatization leads to different reaction pathways. Since the aromaticity of a phenyl ring is stronger than a single aromatic ring of the naphthyl group, C−H bond cleavage occurs and *ortho*-arylated product **C** is formed via successive transmetalation and reductive elimination (**Cycle 1**). On the other hand, 2-naphthyl urea undergoes dearomatization in one aromatic ring, generating benzylic carbocationic species **D**. Intermediate **D** undergoes transmetalation with aryl boronic acids, followed by intramolecular nucleophilic rearrangement and rearomatization to give the final *meta*-arylated product **H** (**Cycle 2** in Scheme 3).[4]

Because heteroarenes have a low degree of aromaticity, we used indole and pyrrole derivatives as the substrates to further study this mechanism. As shown in Scheme 4, using *N*-propyl-2-methylindoles to react with phenylboronic acid **2b** under our reaction conditions, we found the starting material gradually decomposed and no arylated products could be detected. In contrast, changing the indole *N*-substituent to *N*-dimethylcarbomic (**1d**) led to *β*-arylated product **1db** in 33% isolated yield. This result proved the necessity of the directing group for *β*-

Scheme 3. Proposed Mechanism



arylation. As mentioned in Scheme 3, once the *ortho* C−H bond is cleaved, *ortho*-arylation occurs. With a more stable *ortho* C−C bond, dearomatization becomes the only possible pathway. Therefore, *β*-arylated product **1db** could be obtained via **Cycle 2**. Under the same conditions, we changed the substrate to **1e** bearing an an *α*-C−H bond and the *α*-arylated product **1eb** was formed exclusively in 42% isolated yield, indicating the formation of *α*-C−Pd bond and its tendency in *ortho* C−H bond arylation versus *β*-arylation and dearomatization. Because it has been reported that Cu^{2+} could arguably affect the regioselectivity of indole derivatives,[8] we also changed the oxidant to $K_2S_2O_8$ to confirm the *α*- and *β*-regioselectivity. Under condition *b* in Scheme 4, *β*-arylated product **1db** was obtained in 62% isolated yield and *α*-arylated product **1eb** was isolated in 72% yield. It should be stressed that *N*-propyl-2-methylindole was still inert to phenylboronic acid **2b** under condition *b*, even though the solvent was diluted with toluene to avoid its decomposition (condition *c*). Pyrrole derivatives were also tested under these two conditions. Although most of the starting material **1g** decomposed under the oxidative conditions, *α*-arylated *N*-pyrrole carbamate **1gb** was isolated in 16% and 6% yields under condition *a* and *b*, respectively. Using 2,5-dimethyl pyrrole carbamate as the substrate, decomposition of **1f** proceeded very rapidly in the presence of $PhCO_3Bu$-*t* and $Cu(OAc)_2·H_2O$, but *β*-arylated product **1fb** was obtained in

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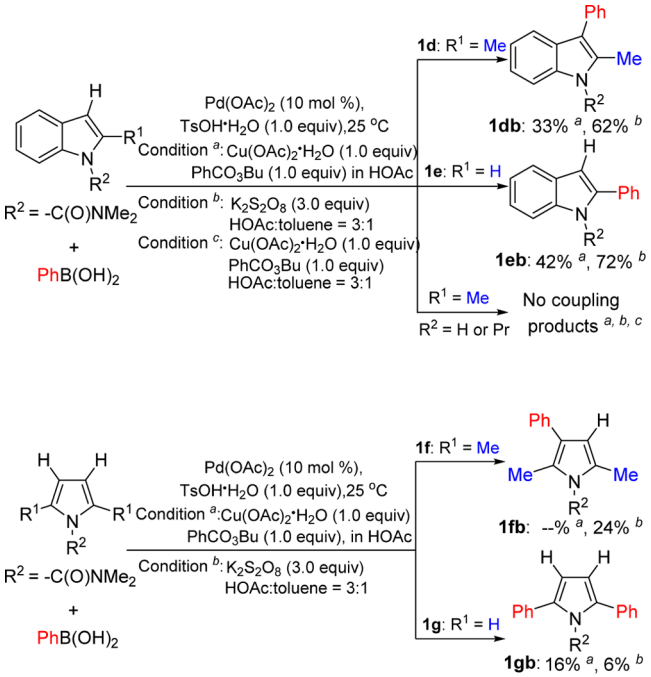
Scheme 4. Regioselective Direct Arylation of Indole and Pyrrole Derivatives under Different Conditions



24% isolated yield when $K_2S_2O_8$ was used as the oxidant (Condition *b*). These results are similar to those obtained in the indole experiments and are consistent with our proposed mechanism.

In conclusion, we have developed a method for the direct *meta*-arylation of 1,1-dimethyl-3-(naphthalen-2-yl) urea. The reaction proceeded in an *ortho*-metalation/*meta*-direct arylation process. By comparing the regiochemical outcome in the direct arylation of 2-naphthyl urea versus phenyl, the important relationship between substrate aromaticity and selectivity became clear. This finding was further confirmed by performing the direct arylation of indole and pyrrole derivatives with aryl boronic acid. This finding will be potentially helpful for remote C−H bond functionalization of diverse polyaromatics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03153.

Experimental procedures and characterization data for new compounds (PDF)

Crystallographic data for **3ah** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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