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C–H Activation

Palladium-Catalyzed Direct Arylation of (Hetero)Arenes with Aryl Boronic Acids[**]

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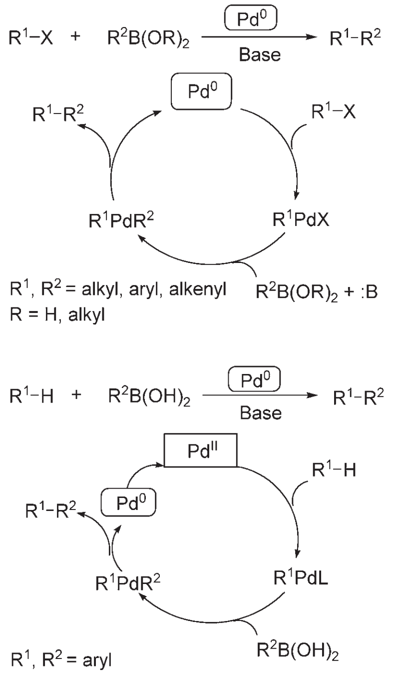
With the development of chemical sciences, the discovery of green and sustainable transformations has been identified as a major challenge for organic chemists. It is no longer appropriate just to produce the organic compounds, but it is important also to generate the products in the most efficient and environmentally friendly way. Direct transformation of a C–H bond into a C–C bond is a relatively clean and efficient method for meeting such goals.[1] In the past few decades, well developed processes have been reported for the transformation of aromatic C–H bonds to C–C bonds and C–X bonds, including catalytic processes utilizing metal complexes such as Ru, Rh, and Pd.[2] Herein we describe a recent observation involving direct construction of biaryl C–C bonds by a Pd^{II}-catalyzed cross coupling of electron-rich (hetero)arenes with aryl boronic acids.

Suzuki–Miyaura coupling is a powerful method that has been widely used to construct biaryls in the syntheses of natural products, synthetic drugs, and materials.[3] Generally, reaction occurs between sp^2 C–X (X = I, Br, OTf, etc) bonds and organoboronic acids or organoboronic esters.[4] Recent developments to make the coupling more practical include using aryl C–Cl, C–OTs, and alkyl C–X (X = halide) bonds.[5] Compared to the traditional Suzuki–Miyaura coupling, which requires aryl halides, direct arylation of arenes with boronic acids offers an efficient way to form C–C bonds. Direct arylation does not require aryl halides as the coupling partner (although most of aryl boronic acids are made from halides).[6] Undoubtedly, direct arylation cannot replace the powerful Suzuki–Miyaura coupling, but in some cases this improvement does address three issues that make it attractive for sustainable chemistry: 1) organic halides are much more expensive than the corresponding arenes; 2) halides are not friendly to the environment; 3) the processes using halides generate undesirable waste products (Scheme 1).



Scheme 1. Top: Traditional Suzuki–Miyaura coupling. Bottom: Direct cross-coupling between C–H bonds and C–B bonds.

Recent efforts have been made towards the direct cross coupling of boronic acid derivatives with C–H bonds. Murai and co-workers made a significant contribution with the direct arylation of acetophenones with boronic esters catalyzed by Ru^0.[7] Yu and co-workers reported the *ortho* alkylation and arylation at sp^2 or sp^3 C–H centers with boronic acids and boronic esters;[8] the substrates had special directing groups such as pyridinyl and carboxylic acids. Sames and co-workers also reported the arylation at an sp^3 C–H center, adjacent to the nitrogen atom of piperidine, with aryl boronic esters using a Ru^0 catalyst.[9] We reported direct arylation at sp^2 C–H centers, *ortho* to an *N*-alkyl acetamino group, with free boronic acids by a Pd^{II} catalyst in the presence of $Cu(OTf)_2$ and Ag_2O.[10] Although these cross-couplings between C–H bonds and boronic acids advanced the traditional Suzuki–Miyaura coupling, the relatively low yields, the requirement of a directing group, and the complex reaction conditions make them less attractive for real applications.

Our goal was to search for new transformations to make the Pd^{II}-catalyzed cross-coupling between general C–H bonds

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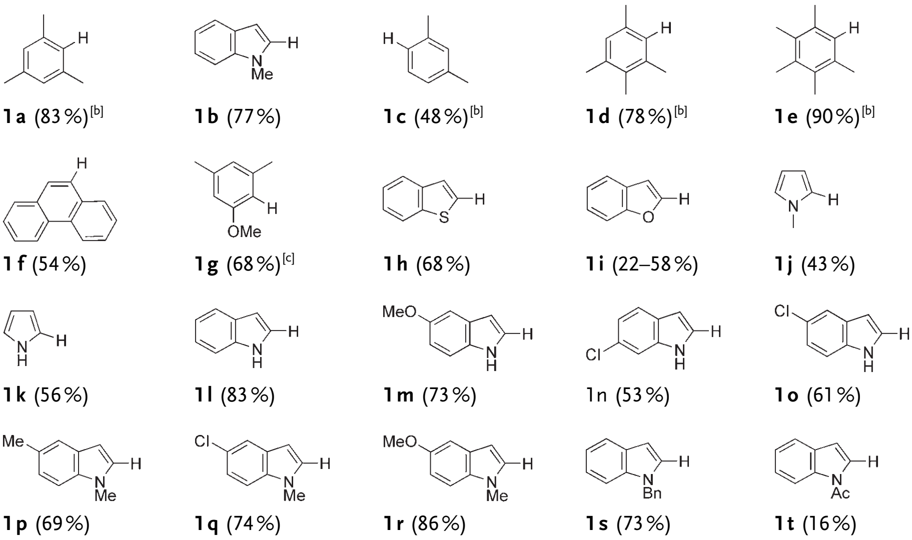
and aryl boronic acids more efficient and practical (Scheme 1). Many challenges need to be addressed for this process to work: 1) Pd^{II}-catalyzed electrophilic C–H functionalization is typically promoted by acidic conditions, whereas the traditional Suzuki–Miyaura coupling with aryl boronic acids occurs under basic conditions; 2) the homocoupling of aryl boronic acids proceeds readily in the presence of a Pd^{II} species,[11] therefore the reaction conditions need to facilitate fast electrophilic attack of aromatic ring relative to the transmetallation of the aryl boronic acids to Pd^{II}. Since it is well known that the presence of a base is beneficial for the transmetallation of aryl boronic acids, we assumed that the presence of acid might reduce the rate of transmetallation and facilitate the electrophilic attack.

Table 1: Scope of the Pd^{II}-catalyzed direct coupling with phenyl boronic acid.[a]


1a (83%)[b] **1b** (77%) **1c** (48%)[b] **1d** (78%)[b] **1e** (90%)[b]

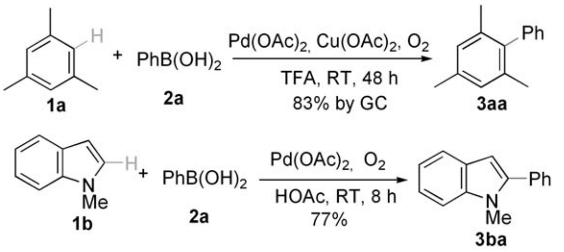
1f (54%) **1g** (68%)[c] **1h** (68%) **1i** (22–58%) **1j** (43%)

1k (56%) **1l** (83%) **1m** (73%) **1n** (53%) **1o** (61%)

1p (69%) **1q** (74%) **1r** (86%) **1s** (73%) **1t** (16%)

[a] Reaction conditions: **1a**, **1c–g** (1.0 mmol), **2a** (0.5 mmol), Pd(OAc)$_2$ (5.0 mol%), Cu(OAc)$_2$ (1.0 equiv) in TFA under 1 atm of O$_2$; **1b**, **1h–t**, **2a** (1.5–2.0 equiv), Pd(OAc)$_2$ (5.0 mol%) in AcOH at room temperature under 1 atm of O$_2$. [b] Yields were determined by GC using *n*-dodecane as an internal standard. [c] The ratio of arylation at the *ortho* and *para* positions was determined to be 2:1 by GC.

With this in mind, we tested the first stoichiometric reaction using mesitylene (**1a**) as the arene substrate with phenyl boronic acid (**2a**) in the presence of 1.0 equivalents of Pd(OAc)$_2$ in trifluoroacetic acid (TFA). Gratifyingly, the coupling product **3aa** was observed by GC, as well as a significant amount of the homocoupling product. Interestingly, a decrease in the amount of Pd(OAc)$_2$ enhanced the ratio of desired product **3aa** to the biphenyl product in the presence of different oxidants. The screening of different conditions revealed Pd(OAc)$_2$ as the best catalyst and dioxygen (O$_2$) as the best terminal oxidant. Under optimal conditions (5.0 mol% of Pd(OAc)$_2$ and 1.0 equiv of Cu(OAc)$_2$ as a cooxidant under an O$_2$ atmosphere) product **3aa** is observed in 83% yield (GC) with a very small amount of biphenyl. Notably, with electron-rich heterocycles as substrates, the reaction conditions were further simplified to include acetic acid (AcOH) as a solvent and O$_2$ as the oxidant (Scheme 2) at room temperature. PtCl$_2$, PtCl$_4$, and AuCl$_3$ were reported as good electrophilic catalysts to activate electron-rich arenes,[12] but low efficiencies were observed and may arise from their poor catalytic ability in coupling reactions with aryl boronic acids.

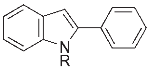
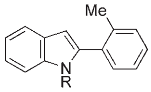
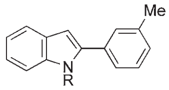
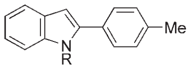
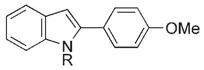
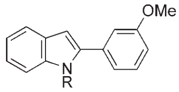
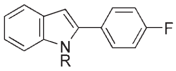
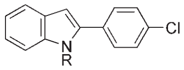
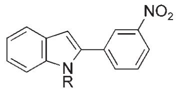
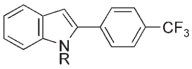
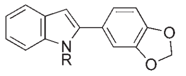
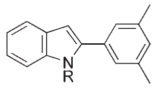


Scheme 2. Direct phenylation of mesitylene (**1a**) and *N*-methylindole (**1b**) with phenyl boronic acid (**2a**).

The substrate scope of the arenes shown above is quite broad (Table 1). In general, electron-rich arenes showed good reactivity with phenyl boronic acid (**2a**), and the corresponding phenylated products **3** were obtained in good yields. The reaction tolerated different functional groups, such as a methyl ether (**1g**), and 2,3-benzothiophene (**1h**) and 2,3-benzofuran (**1i**) were phenylated at the 2-position in excellent regioselectivity. Moreover, N-heterocyles, such as pyrroles **1j**,**k** and indoles **1b** and **1l–s**, were only monophenylated. No protection was required for the arylation of pyrrole **1k** and indoles **1l–o**. Although the groups of Sames and Sanford have recently reported the arylation of indoles with aryl halides,[13] the reaction reported herein is simpler and proceeds under milder conditions. The groups of Fagnou and others recently reported elegant arylations of heterocycles with benzene through a new strategy;[14] Fagnou reported that regioselectivities were controlled by different additives.[14c] However, our method has a broader substrate scope (heterocycles and electron-rich arenes all work in our case) and performs well under mild conditions. In our case, more functionalized indole derivatives (**1m–s**) can be arylated at the 2-position in high efficiency, excellent selectivity, and good yields of isolated products. Substrates **1n**, **1o**, and **1q** show that C–Cl bonds are tolerated and allow for further functionalization.[15] N-acetyl protection (**1t**) significantly decreased the efficiency of the reaction.

The tolerance of functionality on the aryl boronic acids was investigated (Table 2), and we found that: 1) electron-rich substituents were beneficial for the transformation, but, the amount of homocoupling product was also increased;

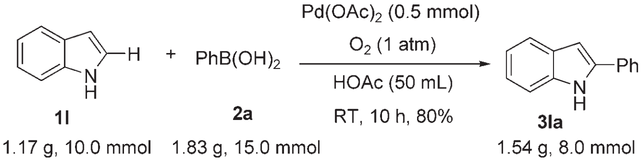
Table 2: Pd^{II}-catalyzed direct arylation of indole **1l** and *N*-methylindole **1b** with various aryl boronic acids.[a]

 R = H, **3la**, 83% Me, **3ba**, 77%	 R = H, **3lb**, 50% Me, **3bb**, 87%	 R = H, **3lc**, 73% Me, **3bc**, 87%
 R = H, **3ld**, 74% Me, **3bd**, 65%	 R = H, **3le**, 53% Me, **3be**, 84%	 R = H, **3lf**, 60% Me, **3bf**, 84%
 R = H, **3lg**, 77%[b] Me, **3bg**, 82%	 R = H, **3lh**, 77%[b] Me, **3bh**, 68%	 R = H, **3li**, 82%[b] Me, **3bi**, 63%
 R = H, **3lj**, 59%[b] Me, **3bj**, 78%	 R = H, **3lk**, 53% Me, **3bk**, 62%	 R = H, **3ll**, 62%[b] Me, **3bl**, 50%

[a] Reaction conditions: aryl boronic acid (1.5–2.0 equiv) and $Pd(OAc)_2$ (5.0 mol%) in AcOH at room temperature under 1 atm of O_2. [b] 10 mol% $Pd(OAc)_2$ catalyst used.

2) when free indole was used as the substrate the efficiency of the transformation was sensitive to steric hindrance of the aromatic boronic acid: *ortho* substituents resulted in a low yield (**3lb**). In contrast, the efficiency of the arylation of *N*-methylindole was not affected by this steric hindrance, as *ortho*-substituted aryl boronic acids gave a higher yield relative to *para* substituted aryl boronic acids (compare **3bb** and **3bd**); 3) C–X (X = F, Cl) groups on the aryl boronic acids were tolerated under the reaction conditions (**3lg**, **3lh**, **3bg**, and **3bh**).

Under mild conditions, the reaction could be scaled up, (Scheme 3; 10.0 mmol of free indole (**1l**) in the presence of 15.0 mmol of phenyl boronic acid (**2a**) and 0.5 mmol of $Pd(OAc)_2$ in 50 mL of AcOH). The reaction was complete after stirring for 10 hours at room temperature under an O_2 atmosphere (1 atm). The AcOH was recovered and the product **3la** was purified by extraction with CH_2Cl_2 in 80% yield. The palladium catalyst was recovered by precipitation and subsequent neutralization. The transformation is amenable to large scale production.



Scheme 3. Phenylation of indole **1l** can be scaled up to 10.0 mmol in the presence of **2** (1.5 equiv) and $Pd(OAc)_2$ (0.5 mmol) in AcOH at room temperature under 1 atm of O_2. Product **3la** was isolated in 80% yield and the AcOH and $Pd(OAc)_2$ were recovered.

We propose a mechanism based on the observation that electron-rich arenes are more efficient than electron deficient arenes. This result suggests that the electrophilic activation of aromatic C–H bonds by Pd^{II} species proceeds as described previously.[2d] To understand this transformation better, we prepared a $PhPdL_2I$ species[16] and used it in a coupling reaction with phenyl boronic acid (**2a**) under our optimized conditions. No coupling was observed with electron-rich arenes, such as mesitylene (**1a**), leading us to hypothesize that the aryl palladium species generated from electrophilic attack is a key intermediate. After the transmetallation of the aryl palladium species by aryl boronic acid, the desired product is produced through reductive elimination. Pd^0 is reoxidized by O_2 or a Cu^{II} species to complete the catalytic cycle.

In summary, we have demonstrated a novel method for the direct construction of biaryl C–C bonds by a Pd^{II}-catalyzed cross coupling of (hetero)arenes and various aryl boronic acids. O_2 is used in the transformation as the final oxidant in acidic media. Various aromatic rings show good selectivities, without requiring directing groups, under mild conditions. Substituents on the boronic acids are tolerated and electron-rich heterocycles, such as indole, pyrrole, and benzofuran, are readily employed in the coupling reaction. The selectivity of the reaction appears to be controlled by the electronic properties of the arenes. Preliminary mechanistic studies suggest that the catalytic cycle is initiated by electrophilic attack of Pd^{II} on the arene, with subsequent transmetallation and reductive elimination to produce the desired products. This new reactivity is anticipated to provide opportunities for further development of clean and sustainable catalytic transformations.

Experimental Section

All the reactions were carried out under a dry oxygen atmosphere. TFA was used without further purification. $Pd(OAc)_2$ was purchased from Alfa Aesar Chemical.

General procedure for arylation of mesitylene (**1a**): Mesitylene (**1a**) (120.0 mg, 1.0 mmol, 2.0 equiv), phenyl boronic acid (**2a**) (61 mg, 0.5 mmol, 1.0 equiv), $Cu(OAc)_2$ (91.0 mg, 0.5 mmol, 1.0 equiv), and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 0.05 equiv) were added to a Schlenck tube. TFA (5.0 mL) was added by syringe and the reaction solution was degassed twice and refilled with O_2 (1.0 atm). The reaction mixture was stirred for 48 h at room temperature. TFA was distilled under reduced pressure and recovered. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with aqueous $NaHCO_3$ (2 × 30 mL). The organic layer was dried over $MgSO_4$ and the desired product **3aa** was identified by GC using n-dodecane as an internal standard.

General procedure for 2-arylation of 1-methylindole (**1b**): 1-Methylindole (**1b**) (65.5 mg, 0.5 mmol, 1.0 equiv), phenyl boronic acid (**2a**) (91.5 mg, 0.75 mmol, 1.5 equiv), and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 0.05 equiv) were added to a Schlenck tube. AcOH (5.0 mL) was added by syringe and the resulting solution was degassed twice and refilled with O_2 (1.0 atm). The mixture was stirred for 6–8 h at room temperature. AcOH was recovered by distillation under reduced pressure, and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with aqueous $NaHCO_3$ (2 × 30 mL). The organic layer was dried over $MgSO_4$. After removal of the solvent, product **3ba** was purified by flash chromatography on silica gel (hexanes/dichloromethane = 10:1 as an eluent) and isolated in 77% yield.

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