Palladium Catalysis

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Suzuki–Miyaura Coupling Reaction by Pd^{II}-Catalyzed Aromatic C–H Bond Activation Directed by an *N*-Alkyl Acetamino Group**

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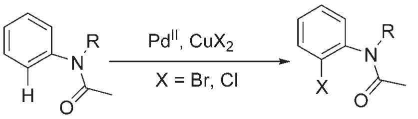
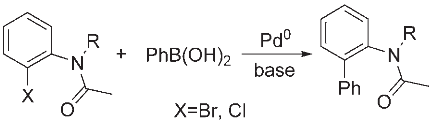
C–C bond formation is an important process in organic synthesis. The Suzuki–Miyaura coupling is one of the most useful methods to construct C–C bonds and has been broadly applied in syntheses of natural products, synthetic drugs, and materials.[1] In a traditional palladium-catalyzed Suzuki–Miyaura coupling, C–X (X = Br, I, OTf; Tf = trifluoromethanesulfonyl) groups were required as substrates to initiate the oxidative addition of Pd^0 to produce Pd^{II}-containing intermediates. Recent advances have allowed the use of the relatively cheap and readily available organic chlorides,[2] but an ideal and environmentally friendly method to construct C–C bonds would be the direct functionalization of C–H bonds.

Over the past several decades, extensive efforts have been made to develop a transition-metal-catalyzed C–H functionalization.[3] Direct arylation of aromatic C–H bonds has been developed with or without directing groups to construct a biaryl structural motif, which is an important scaffold in many pharmaceutically relevant and biologically active compounds.[4] In many cases, C–H bond activation by transition-metal complexes can offer a direct route to C–M (M = metal) intermediates that are also accessible through the oxidative addition of a low-valent transition-metal complex to organic halides. However, the direct activation of C–H bonds could lead to the same valuable products but avoid the requirement of the presence of halides in the starting material. Although the C–C bond could be constructed by transition-metal-catalyzed C–H bond activation of arenes by using other methods,[5] processes to form C–C bonds by Suzuki–Miyaura-type coupling were rarely reported. Very recently, the research group of Yu reported the alkylation of sp^3 or sp^2 C–H bond directed by pyridinyl and carboxylic groups.[6] A number of research groups, including that of Sames, have reported the arylation of sp^3 C–H bonds catalyzed by ruthenium complexes with an aromatic boronic ester and by using a heterocyclic directing group.[7] Herein we report a palladium-catalyzed C–C bond formation to afford highly regioselective *ortho* arylation of aromatic C–H bond in a Suzuki—Miyaura-type coupling reaction with aromatic boronic acids directed by an acetyl amino group.

We previously developed a highly regioselective halogenation of acetanilides by using a Pd^{II}-catalyzed reaction [Eq. (1)].[8] A Suzuki–Miyaura coupling reaction mediated by Pd could occur from this halide under basic conditions [Eq. (2)].[9] In our halogenation reaction, we proposed the palladacycle **5** as a key intermediate, identical to that generated from the oxidative addition of **4** to Pd^0 in the traditional Suzuki–Miyaura coupling. This intermediate **5**, if formed, will undergo transmetalation with boronic acids and reductively eliminate to form the C–C bond. Thus, we hypothesized that a Suzuki–Miyaura coupling by using C–H functionalization of acetanilides with aryl boronic acids might proceed under the proper conditions (Scheme 1).



(1)



(2)

However, the reaction conditions of the halogenation reaction and Suzuki–Miyaura coupling may not be compatible because, although both may go through the same intermediate **5**, they were catalyzed by different palladium species. The halogenation was carried out under acidic conditions to enhance the electrophilic ability of the Pd^{II} species that is important for cyclopalladation. However, most Suzuki–Miyaura couplings proceed under basic conditions.[1,2] This difference makes it difficult to combine these two processes and construct a C–C bond from a C–H bond. We have to overcome this problem if we want to directly

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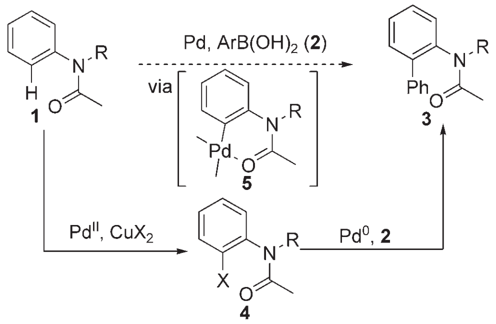
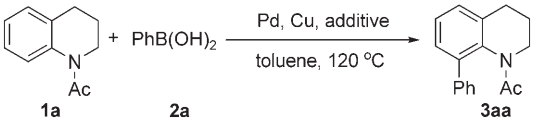


Scheme 1. Design of a direct Suzuki–Miyaura coupling reaction with a Pd-catalyzed C–H bond activation.

construct C–C bonds by functionalization of C–H bonds with palladium.

We first attempted the coupling reaction with phenylboronic acid **2a** as a reagent. The substrate **1a** was chosen because of its high reactivity in the halogenation reaction, and the chlorination was first surveyed with $Cu(OAc)_2$ as the oxidant. Unfortunately, the desired coupling product was not observed and only biphenyl was produced as a homocoupling product of phenylboronic acid (Table 1, entries 2 and 3). However, $Cu(OTf)_2$ was found to be a sufficient oxidant for this transformation and the desired product **3aa** was observed in 37% yield (calculated from GC) with a large amount of biphenyl as by-product (Table 1, entry 4). Since additives are important to inhibit the homocoupling in Suzuki–Miyaura coupling reactions, several different additives were tested in our reaction system.[2,10] Gratifyingly, Ag_2O was found to be the most efficient additive in our system and may work as either a co-oxidant, base, or both (Table 1, entry 6).

Table 1: Suzuki reaction under various conditions with C–H activation.[a]



Entry	Pd cat. (mol%)	Cu^{II} salt (equiv)	Additive (equiv)	**3aa** [%][b]
1	$Pd(OAc)_2$ (5.0)	–	–	< 5
2	$Pd(OAc)_2$ (5.0)	$Cu(OAc)_2$ (1.0)	–	< 5
3	$Pd(OAc)_2$ (5.0)	$Cu(OAc)_2$ (1.0)	Cu_2O (1.0)	< 5
4	$Pd(OAc)_2$ (5.0)	$Cu(OTf)_2$ (1.0)	–	37
5	$Pd(OAc)_2$ (5.0)	$Cu(OTf)_2$ (1.0)	Cu_2O (1.0)	37
6[c]	$Pd(OAc)_2$ (5.0)	$Cu(OTf)_2$ (1.0)	Ag_2O (1.0)	85
7	$Pd(OAc)_2$ (5.0)	$Cu(OAc)_2$ (1.0)	Ag_2O (1.0)	< 5
8	$Pd(OAc)_2$ (5.0)	$[Cu(acac)_2]$ (1.0)	Ag_2O (1.0)	< 5
9	$Pd(OAc)_2$ (5.0)	$PhI(OAc)_2$ (1.0)	Ag_2O (1.0)	< 5
10	$Pd(OAc)_2$ (5.0)	1,4-benzoquilone (1.0)	Ag_2O (1.0)	< 5
11	$Pd(OAc)_2$ (5.0)	oxone (0.5)	Ag_2O (1.0)	< 5
12	$Pd(OTFA)_2$ (5.0)	$Cu(OTf)_2$ (1.0)	Ag_2O (1.0)	71
13	$PdCl_2$ (5.0)	$Cu(OTf)_2$ (1.0)	Ag_2O (1.0)	6
14	$[Pd(PhCN)_2Cl_2]$ (5.0)	$Cu(OTf)_2$ (1.0)	Ag_2O (1.0)	12
15	$[Pd(PPh_3)_2Cl_2]$ (5.0)	$Cu(OTf)_2$ (1.0)	Ag_2O (1.0)	16
16	$[Pd(dba)_2]$[d]	$Cu(OTf)_2$ (1.0)	Ag_2O (1.0)	59
17	–	$Cu(OTf)_2$ (1.0)	Ag_2O (1.0)	< 5
18	$Pd(OAc)_2$ (5.0)	–	Ag_2O (1.0)	< 5

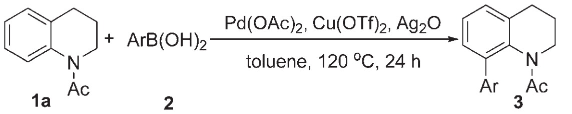
[a] All the reactions were carried out with **1a** (0.2 mmol) with phenylboronic acid (0.4 mmol) under standard conditions; acac = acetylacetonate, OTFA = trifluoroacetate, Tf = trifluoromethanesulfonyl. [b] Yields calculated from GC using *n*-dodecane as an internal standard. [c] Yield of isolated product. [d] dba = *trans,trans*-dibenzylideneacetone.

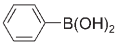
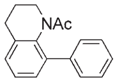
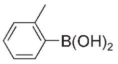
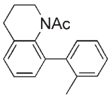
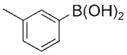
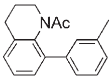
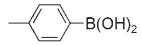
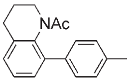
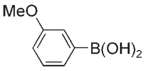
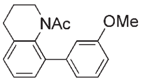
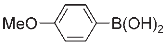
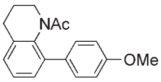
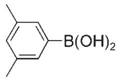
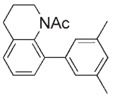
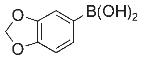
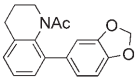
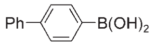
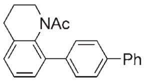
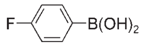
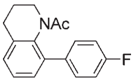
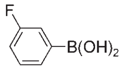
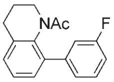
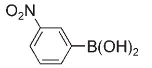
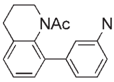
With other copper salts, such as $Cu(OAc)_2$ and $[Cu(acac)_2]$, the reaction did not proceed well (Table 1, entries 7 and 8). Other common inorganic and organic oxidants were not efficient for this transformation (Table 1, entries 9–11). Different palladium species were also tested. $Pd(OTFA)_2$ had a comparable catalytic reactivity for this transformation (Table 1, entry 12). The efficiency with $[Pd(PhCN)_2Cl_2]$, $PdCl_2$, or $[Pd(PPh_3)_2Cl_2]$ was much lower than that with $Pd(OAc)_2$ (Table 1, entries 6 and 13–15). We hypothesized that the catalytic efficiency of the Pd^{II} species arose from both its electrophility and solubility. Pd^0 species, such as $[Pd(dba)_2]$, could also act as a catalyst with good efficiency, and is presumably oxidized to Pd^{II} under the oxidation conditions employed (Table 1, entry 16). Of the solvents surveyed, only toluene was found to be successful for the transformation. Interestingly, the standard conditions reported by the research group of Yu for the alkylation directed by a pyridinyl group was also applied into this system, but only the homocoupling biphenyl product was observed.[6]

After screening of the reaction conditions, the substrate scope was studied. Different aromatic boronic acids were submitted to the reaction with **1a** (Table 2). We found three trends: 1) Different substituents on the aromatic ring of the boronic acids were compatible with the arylation. Monosubstituted electron-donating groups helped increase the efficiency, and the products **3** were produced in good to excellent yields (Table 2, entries 1 and 3–6), whereas electron-withdrawing groups were found to decrease the yields (entries 10–12). 2) The position of the substituents on the phenyl ring of the boronic acids played a vital role and *meta* or *para* substituents provided the best yields. When *ortho*-substituted boronic acids (for example, *ortho*-tolylboronic acid) were used, the coupling reaction did not proceed well and mainly the starting materials were recovered (Table 2, entry 2). 3) The use of disubstituted aryl boronic acids was found to decrease the efficiency of the transformation, which may be due to steric hindrance (Table 2, entries 7 and 8).

Various *N*-alkyl acetanilides were investigated (Table 3). An alkyl group could be introduced into either the phenyl or aliphatic ring of 1,2,3,4-tetrahydroquniline, and all of the coupling reactions performed well. The desired products **3ba**–**3fa** were isolated in excellent yields (Table 3, entries 2–6). Notably, arylation only occurred on the scaffold of 1,2,3,4-tetrahydroquniline when there was a phenyl group in the side chain (Table 3, entry 5). *N*-Acetyl-2,3-dihydroindole and its derivatives were also good substrates for this transformation (Table 3, entries 7–10). The relatively hindered *N*-acetyl-2-methyl-2,3-dihydroindole could be used with **2a** to give the coupling products **3ha** and **3ja** in moderate to excellent yields (Table 3, entries 8 and 10). Notably, the relatively stable chloride group can survive the mild reaction conditions and is available for further functionalization (Table 3, entry 10).[2] Moreover, the acetyl directing group is key for the coupling reaction, and when the non-acetylated 2,3-hydroindole was used, the desired coupling product was not observed.[11]

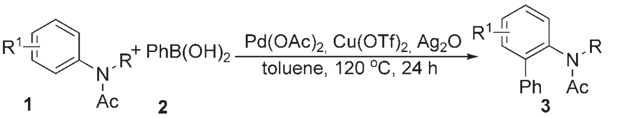
Table 2: Suzuki–Miyaura coupling of **1a** with various boronic acids **2**.[a]

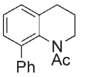
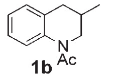
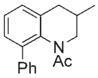
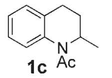
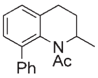
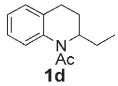
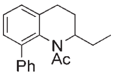
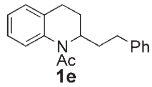
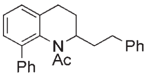
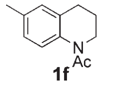
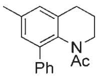
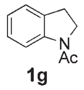
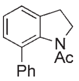
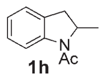
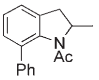
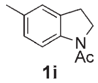
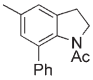
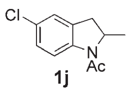
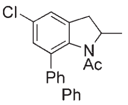
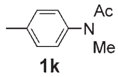
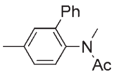
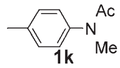
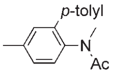


Entry	2	3	Product (yield [%])[b]
1	 **2a**		**3aa** (85)
2	 **2b**		**3ab** (20)[c]
3	 **2c**		**3ac** (82)
4	 **2d**		**3ad** (74)
5	 **2e**		**3ae** (80)
6	 **2f**		**3af** (75)
7	 **2g**		**3ag** (35)[c]
8	 **2h**		**3ah** (33)[c]
9	 **2i**		**3ai** (58)
10	 **2j**		**3aj** (62)
11	 **2k**		**3ak** (48)
12	 **2l**		**3al** (31)[c]

[a] All the reactions were carried out with **1a** (0.2 mmol) and boronic acid **2** (0.4 mmol) in the presence of Pd(OAc)$_2$ (5.0 mol%), Cu(OTf)$_2$ (1.0 equiv), and Ag$_2$O (1.0 equiv). [b] Yields of isolated products are the average of at least two experiments. [c] Some starting material **1a** was also recovered during these reactions.

Table 3: Suzuki–Miraura coupling of various acetyl amides with **2a**.[a]

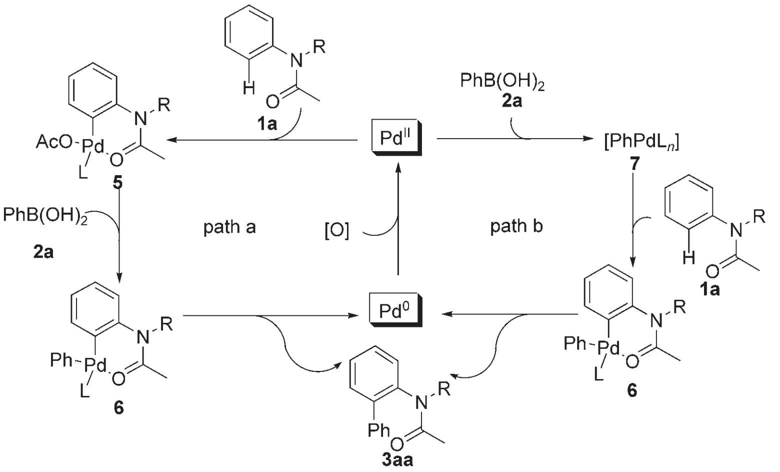


Entry	1	3	Product (yield [%])[b]
1			**3aa** (85)
2			**3ba** (56)
3			**3ca** (78)
4			**3da** (76)
5			**3ea** (70)
6			**3 fa** (70)
7			**3ga** (84)
8			**3ha** (92)
9			**3ia** (82)
10			**3ja** (41)
11[c]			**3ka** (66)
12[c,d]			**3kb** (72)

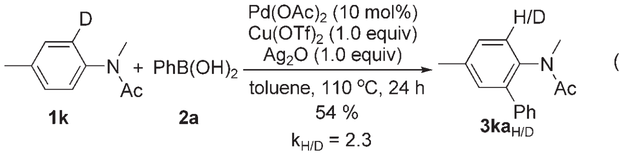
[a] All the reactions were carried out with **1** (0.2 mmol) and **2a** (0.4 mmol) in the presence of Pd(OAc)$_2$ (5 mol%), Cu(OTf)$_2$ (1.0 equiv), and Ag$_2$O (1.0 equiv) in toluene (4 mL) at 120°C, unless otherwise stated. [b] Yields of isolated products are the average of at least two experiments. [c] 1,2,4-Trimethylbenzene was used as a solvent. [d] *Para*-tolylboronic acid **2d** was used.

The coupling reaction may be initiated by electrophilic attack of a Pd^{II} center to the aromatic ring with the assistance of the acetamino group, followed by transmetalation and reductive elimination to produce the expected product (Scheme 2, path a). The other possibility is the transmetalation of the boronic acid with Pd^{II} salts to form initially an arylated Pd^{II} species,[12] which may attack in an electrophilic manner to the aromatic ring to form a diaryl palladium species, which then would undergo reductive elimination to give the final product (Scheme 2, path b).

To further understand this transformation, we carried out some preliminary mechanistic studies. An intramolecular isotopic effect ($K_{H/D} = 2.3$) indicated that the cleavage of a C–H bond was involved in the rate-determining step [Eq. (3)]. If the reaction mixture with no added boronic acid **2a** but with a stoichiometric amount of Pd(OAc)$_2$ was allowed to react for one hour, after the addition of **2a**, the coupling product was isolated in good yield. In contrast, similar treatment of the reaction mixture without acetanilide **1a** only gave the homocoupling product with no observation of the desired

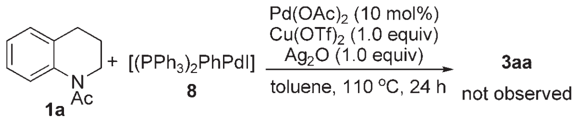


Scheme 2. Proposed mechanism of the reaction. L = ligand.



(3)

product. We hypothesized that the electrophilic ability of the intermediate **7** from the direct transmetalation was inhibited by increased electron density on the Pd^{II} center with an aryl group. A second transmetalation with an additional molecule of boronic acid occurred to form the homocoupling by-product.[8] Another plausible pathway for this transformation involves the formation of the key intermediate **6** from the transmetalation between **5** and the {Ph–Pd} species **7**, based on the recent studies in palladium chemistry.[13] However, the reaction using $[(PPh_3)_2PhPdI]$ (**8**) did not proceed well under the standard conditions [Eq. (4)].[14] Thus, we favor the Pd^{II}/Pd^0 catalytic cycle shown in path a (Scheme 2) although other possibilities can not be ruled out.[15] Further investigations to understand this mechanism are underway.



(4)

In summary, we have developed an efficient and clean method to construct C–C bonds from *N*-alkyl acetanilides and aryl boronic acids catalyzed by a Pd^{II} species by direct C–H bond functionalization. This development also offers a new strategy to construct complicated structures by Suzuki–Miyaura coupling under a halogen-free process. Further applications of this transformation to organic syntheses is underway in our group.

Experimental Section

General: All reactions were carried out in a stoppered Schlenk flask under air. All the chemicals were purchased from Alfa Aesar and Acros Chemical, and used without further purification. Toluene was freshly distilled over sodium with the use of diphenyl ketone as an indicator. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Varian 300 M spectrometers with $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. Chemical shifts are reported in ppm by assigning TMS resonance in the ^1H NMR spectrum as 0.00 ppm and $CDCl_3$ resonance in the ^{13}C spectrum as 77.0 ppm. All coupling constants (*J* values) were reported in Hertz (Hz). Column chromatography was performed on silica gel 200–300 mesh. IR, X-ray, GC, MS, and HRMS were performed at the State-Authorized Analytical Center at Peking University.

General procedure: $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), $Cu(OTf)_2$ (72.4 mg, 0.2 mmol), Ag_2O (46.4 mg, 0.2 mmol), and freshly distilled toluene (4 mL) were added to a dry Schlenk tube. The acetanilide **1** (0.2 mmol) was then added, followed by the boronic acid **2** (0.4 mmol). The reaction mixture was heated and stirred for 24 h at 115 °C in an oil bath and the progress of the reaction monitored by thin-layer chromatography. Purification of the crude mixture by flash chromatography (petroleum ether/ethyl acetate) gave the desired product **3**.

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Keywords: C–C coupling · C–H activation · electrophilic substitution · palladium · Suzuki–Miyaura reaction

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