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A Palladium/Copper Bimetallic Catalytic System: Dramatic Improvement for Suzuki–Miyaura-Type Direct C–H Arylation of Azoles with Arylboronic Acids

Bo Liu, Xurong Qin, Kaizhi Li, Xiyu Li, Qiang Guo, Jingbo Lan, and Jingsong You*[a]

The Suzuki–Miyaura coupling ranks as one of the most powerful and reliable biaryl forming reactions.[1] Traditionally, these transition-metal catalyzed cross-couplings require aryl halides or pseudohalides to react with boronic acids.[2] As a variety of metal-mediated biaryl formations through aromatic C–H activation have been popularized, the Suzuki–Miyaura-type reactions, in which aryl halides or pseudohalides are replaced by (hetero)arenes, have recently attracted attention. This type of cross-coupling is not only an efficient and complementary process to form biaryls, but also is in connection with sustainable chemistry. Whereas the Suzuki–Miyaura-type direct C–H arylation of arenes (which generally require a directing group) has been developed greatly,[3] the coupling of heteroarenes with arylboronic acids still remains elusive. In comparison with arenes, heteroarenes themselves are susceptible to oxidative homocoupling and decomposition as well as self-coupling of arylboronic acids in the presence of a Pd^{II} species. As far as we know, only a few successful examples relative to heteroarenes have been described so far. Shi et al. described a Pd^{II}-catalyzed cross-coupling of electron-rich heteroarenes (i.e., pyrrole, furan, and thiophene derivatives) with arylboronic acids under mild conditions.[4] Studer et al. reported the first direct C–H arylation of indoles with arylboronic acids and the 2,2,6,6-tetramethylpiperidine *N*-oxyl radical (TEMPO) as an external mild oxidant at room temperature.[5] Although the aryl–azole structural motifs are ubiquitous in biologically important natural products, synthetic pharmaceuticals, and materials,[6] it is unknown that the direct C–H arylation of azoles with arylboronic acid hitherto. In this context, we wish to develop an efficient general methodology to achieve the direct Suzuki–Miyaura-type coupling of a wide range of azoles with arylboronic acids.

Our initial exploration focused on the monometallic palladium(II)-catalyzed C–H arylation of various azoles with arylboronic acids in the presence of inorganic oxidants (e.g., $Cu(OAc)_2$, Ag_2CO_3, and Ag_2O), organic oxidants (e.g., DDQ (2,3-dichloro-5,6-dicyanobenzoquinone), and BQ (benzoquinone)), and/or dioxygen (O_2). Whereas π-electron excessive five-membered heterocycles (i.e., thiophenes, furans, and pyrroles) smoothly coupled with arylboronic acids through an electrophilic mechanism, the azoles investigated herein gave only trace amount to low yields of the desired products.[4,5] Although both types of heteroarenes are electron-rich, the C2 sites of azoles are relatively electron-deficient. We believe that the distinctly differential π-electronic characteristics may induce the clear distinctness of reactivity. Owing to the relatively acidic C2 sites, azoles are unsusceptible to electrophilic C–H substitution (S_EAr) of Pd^{II} under mild conditions. Considering that Cu^I salts have been used as catalysts or activators in direct C–H arylations of azoles,[7] we envisioned whether the additional introduction of a catalyic amount of Cu^I salt could assist the C2–H bond activation to generate an azole–copper species, which could undertake a transmetalation to arylpalladium(II) intermediate to enable a catalytic cycle. Herein, we disclose an efficient palladium/copper co-catalytic system for the direct C–H arylation of a variety of azoles with arylboronic acids to extend current synthetic methodologies.

Xanthines (e.g., caffeine, theophylline, and theobromine) are important biologically active alkaloids with imidazole skeletons. 8-(Hetero)aryl-substituted xanthines are highly potent and selective antagonists at human A_{2B} adenosine receptors.[8] Following our continuing interest in the direct C arylation of xanthines, we initially focused on the heterocoupling of caffeine **1** with phenylboronic acid **2a** (Scheme 1). In this model reaction we screened several parameters (e.g., oxidant, base, solvent, and additive) shown in Table 1.

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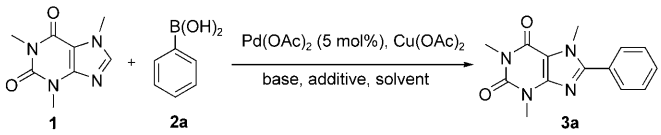


Scheme 1. Direct C–H arylation of caffeine with phenylboronic acid.

Table 1. Optimization of the coupling of caffeine with phenylboronic acid.[a]

Entry	Oxidant	Base	Additive	Solvent	Yield [%][b]
1	BQ	KF	–	DMSO	trace
2	DDQ	KF	–	DMSO	trace
3	O_2	KF	–	DMSO	trace
4	Ag_2O	KF	–	DMSO	trace
5	Ag_2CO_3	KF	–	DMSO	trace
6	$Cu(OAc)_2$	KF	–	DMSO	46
7	$Cu(OAc)_2$	K_3PO_4	–	DMSO	42
8	$Cu(OAc)_2$	Cs_2CO_3	–	DMSO	38
9	$Cu(OAc)_2$	Na_2CO_3	–	DMSO	30
10	$Cu(OAc)_2$	TBAF·$3H_2O$	–	DMSO	trace
11	$Cu(OAc)_2$	KF	–	dioxane	trace
12	$Cu(OAc)_2$	KF	–	*o*-xylene	trace
13	$Cu(OAc)_2$	KF	–	DMF	56
14	$Cu(OAc)_2$	KF	–	NMP	62
15	$Cu(OAc)_2$	KF	CuCl	NMP	76
16	$Cu(OAc)_2$	KF	CuBr	NMP	66
17	$Cu(OAc)_2$	KF	CuCl + BQ	NMP	82[c]

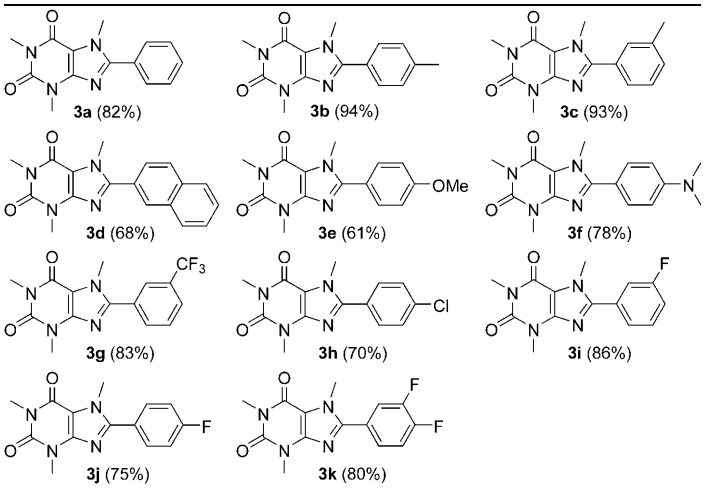
[a] Reactions were carried out by using $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1 equiv), base (1 equiv), copper(I) salt (10 mol%), caffeine (0.5 mmol), and phenylboronic acid (1 mmol) in a 0.5 M solution for 30 h at 80 °C. [b] Isolated yields. [c] 0.5 equiv of BQ. DMSO = dimethyl sulfoxide, TBAF = *tetra*-*n*-butylammonium fluoride, DMF = *N*,*N*-dimethylformamide, NMP = *N*-methyl-2-pyrrolidone.

Among the oxidants investigated, $Cu(OAc)_2$ was the best choice (Table 1, entries 1–6). After screening a variety of bases (e.g., KF, K_3PO_4, Cs_2CO_3, Na_2CO_3, and TBAF·$3H_2O$), KF was found to be the most effective (Table 1, entries 6–10). Subsequently, a 62% yield of heterocoupling product was obtained in NMP by using one equivalent of KF as the base and $Cu(OAc)_2$ as the oxidant (Table 1, entries 6 and 11–14). Excitingly, as a catalytic amount of Cu^I was employed as the co-catalyst, catalytic efficiency could be improved significantly. Copper(I) chloride was proven to be superior to other sources of the copper salt (Table 1, entry 15).

It is well known that the transmetalation between arylboronic acids and Pd^{II} species readily leads to undesired homocoupling of arylboronic acids, which suppresses the generation of the cross-coupling product. BQ has been widely used as the oxidant or additive in some oxidative cross-coupling reactions. To our delight, addition of BQ restrained the homocoupling to improve the yield of target compound upon to 82% (Table 1, entry 17). Thus, the best result was obtained by using 1 equiv of $Cu(OAc)_2$ as the oxidant, 1 equiv of KF as the base, and 0.5 equiv of BQ as the additive in the presence of bimetallic catalytic system of $Pd(OAc)_2$ (5 mol%) and CuCl (10 mol%) in NMP at 80 °C for 30 h.

With optimized conditions now in hand, we explored the scope of this methodology with respect to arylboronic acid structure as summarized in Table 2. It was gratifying to find

Table 2. Catalytic C arylation of caffeine with various arylboronic acids.[a]



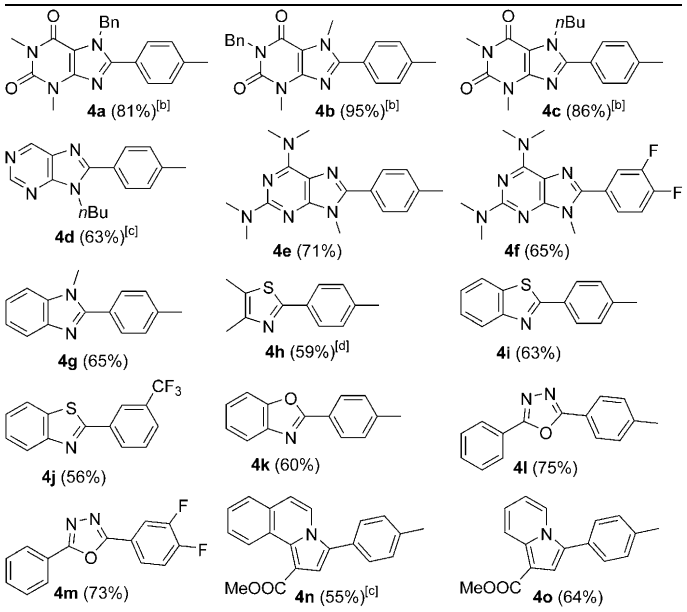
[a] Conditions: Reactions were carried out by using $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1 equiv), KF (1 equiv), CuCl (10 mmol%), BQ (0.5 equiv), caffeine (0.5 mmol), and arylboronic acid (1.0 mmol) in a 0.5 M NMP solution for 30 h at 80 °C (isolated yields in parentheses).

that our catalyst system accelerated the arylation of caffeine with a wide array of arylboronic acids. Whether the arylboronic acids were electron-rich or electron-poor, all of them afforded good to excellent yields (Table 2, **3a–k**). Owing to the importance of fluorobiaryl products in medicinal and materials chemistry, fluoroarylboronic acids were investigated accordingly. The reaction conditions were also suitable for a variety of fluoroarylboronic acids (Table 2, **3i–k**).

We next applied this protocol to other xanthines to prepare 8-aryl theophylline and theobromine derivatives in good to excellent yields (Table 3, entries **4a–c**). Simple purine heterocycles are attractive as "functional" π components in organic materials with biological relevance.[9] Recently, C arylation of purines has started to attract interest.[10] Our methodology could be applicable to the synthesis of various 8-arylated purines (Table 3, entries **4d–f**). In addition to these important alkaloids, this bimetallic catalytic system was proven to effectively promote the cross-coupling of a relatively wide range of azoles (e.g., benzoimidazole, benzoxazole, thiazoles, and oxadiazoles) with arylboronic acids to give moderate to good yields with excellent regioselectivity (at a relatively acidic C(sp^2) position; Table 3, entries **4g–m**).

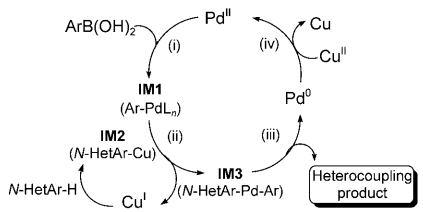
It is important to stress that the cross-coupling reactions of azoles investigated in Table 3 proceeded more sluggishly in the absence of CuCl, and the yields of aryl azoles generally decreased to around 15–30%. Based on this observation, this type of Suzuki–Miyaura coupling is assumed to mainly involve two plausible catalytic routes: 1) The CuCl-mediated process might occur through the formation of the azole–

Table 3. Catalytic C arylation of (hetero)arenes with boronic acids.[a]



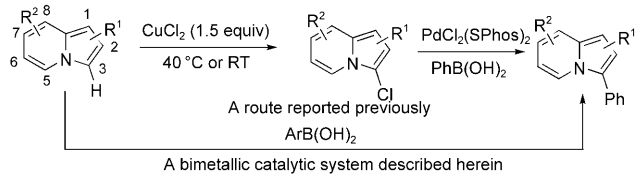
[a] Conditions: Reactions were carried out by using $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1 equiv), KF (1 equiv), CuCl (10 mmol%), BQ (0.5 equiv), heteroarene (0.5 mmol), and arylboronic acid (1.0 mmol) in a 0.5 M NMP solution for 30 h at 100 °C (isolated yields in parentheses). [b] 80 °C. [c] 120 °C. [d] $Cu(PPh_3)_2NO_3$ (10 mmol%) was added instead of CuCl.

copper species **IM2**, and subsequent transmetalation with arylpalladium species **IM1** to form the key heterocoupling intermediate **IM3**, followed by reductive elimination to produce the desired product. Pd^0 could be reoxidized by $Cu(OAc)_2$ to complete the catalytic cycle; 2) Given that other oxidants including inorganic oxidants, organic oxidants, and/or dioxygen mentioned above were completely incapable of fulfilling the catalytic cycle, we rationalized that an (even catalytic) amount of copper(I) formed from $Cu(OAc)_2$ could promote the formation of the azole–copper species to carry out the transmetalation in the absence of CuCl (Scheme 2).[7,11,12]



Scheme 2. Plausible catalytic cycle of Suzuki–Miyaura-type direct C-arylation of azoles with arylboronic acids.

Indolizine derivatives are a type of N-fused heterocycles broadly found in biologically important natural products and synthetic pharmaceuticals.[13] The synthesis of 3-arylated indolizines described previously required two steps, in which indolizine was first pre-activated to 3-chloroindolizine, and then underwent a typical Suzuki–Miyaura coupling with arylboronic acids (Scheme 3).[14] Interestingly, this bimetallic catalytic method was capable of allowing the direct synthesis of 3-arylated indolizines from indolizine through the C–H arylation with arylboronic acids in one step.



Scheme 3. Synthesis of 3-arylated indolizines.

In conclusion, we have developed for the first time a class of Suzuki–Miyaura-type direct C–H arylation of azoles instead of azole halides or pseudohalides with arylboronic acids. The bimetallic catalytic system not only allows the C arylation of a broader spectrum of azoles with various arylboronic acids under relatively mild conditions, but is also applied to the direct synthesis of 3-arylated indolizines from indolizines. We believe that this methodology would provide a powerful complement for the traditional Suzuki–Miyaura coupling reactions.

Experimental Section

A flame-dried Schlenk test tube with a magnetic stirrer bar was charged with $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), N-heteroarene (0.5 mmol), arylboronic acid (1.0 mmol), $Cu(OAc)_2$ (0.5 mmol), CuCl (0.05 mmol), BQ (0.25 mmol), KF (0.5 mmol), and NMP (1.0 mL) under N_2. A rubber septum was replaced with a glass stopper, and the system was then evacuated twice and back-filled with N_2. The reaction mixture was stirred for 5 min at room temperature, and then heated at the indicated temperature for 30 h. The reaction mixture was then cooled to ambient temperature, diluted with CH_2Cl_2 (20 mL), filtered through a celite pad, and washed with CH_2Cl_2 (10–20 mL). The combined organic extracts were concentrated and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

Acknowledgements

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