Cross-Coupling

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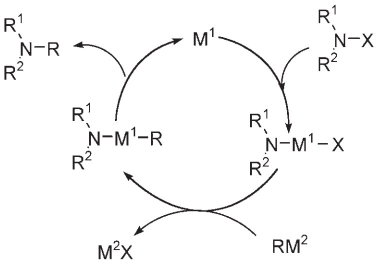
Aryl Halide Tolerated Electrophilic Amination of Arylboronic Acids with *N*-Chloroamides Catalyzed by CuCl at Room Temperature**

*Chuan He, Chong Chen, Jin Cheng, Chao Liu, Wei Liu, Qiang Li, and Aiwen Lei**

Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday

Transition-metal-catalyzed aryl C_{sp2}–N bond formation has been intensively studied over the past decade because of the importance of the amines and their derivatives in chemistry related fields.[1–9] The Pd- or Cu-catalyzed formation of anilines from electrophilic aryl halides and nucleophilic primary or secondary amines, pioneered by Buchwald and co-workers and Louie and Hartwig, as well as others,[10–14] is a hallmark reaction in this field. In 1998, Chan et al., Evans et al., and Lam et al. independently developed Cu-mediated oxidative amination of nucleophilic arylboronic acids with amines or other nucleophiles,[16–20] and the methods were later improved to include catalytic versions.[15,17,21,22] However, electrophilic amination of organometallic reagents by $R^1R^2N^+$ synthons,[23–31] though conceptually feasible, has received much less attention.[32–37] The putative catalytic cycle of this transformation is illustrated in Scheme 1: (1) reaction of R^1R^2N–X (as an electrophile) with the metal catalyst (M^1) would introduce the amine group to the metal center to form R^1R^2N–M^1–X;[34–48] (2) transmetalation of RM^2 ($M^2 = B(OH)_2$) with R^1R^2N–M^1–X to furnish R^1R^2N–M^1R; and (3) final reductive elimination to form the C–N bond. The groups of Liebeskind and Johnson have studied this type of C–N bond formation employing N–O derivatives.[32–37] *N*-Chloroamides, though attractive because of the ease of preparation[49–51] and the high activities of the N–Cl bond,[23,50,51] have seldom been utilized in catalytic electrophilic amination reactions. To the best of our knowledge, Göttlich et al. has primarily studied the Cu-mediated reaction of *N*-chloroamines with alkenes.[38,39,52] Herein, we communicate our results regarding ligandless copper-catalyzed electrophilic amination of arylboronic acids by *N*-chloroamides under mild conditions.



Scheme 1. Putative mechanism of transition-metal-catalyzed electrophilic amination of organometallic reagents by *N*-haloamides.

Our initial experiments of *N*-chloro-*N*-phenylacetamide[49] (**1a**) and phenylboronic acid (**2a**) were carried out by using palladium catalysts. In all attempts, biphenyl was formed instead of the desired N-arylation product (**3a**). However, copper catalysts turned out to be effective, even at room temperature, and CuCl was found to give the best yield when K_3PO_4 was used as the base (Table 1, entries 1–7). Additional screening of different bases revealed that Na_2CO_3 improved the yield to 99%, whereas other bases such as K_2CO_3, Li_2CO_3, and KF etc. were less effective (Table 1, entries 1, and 8–12). The nonpolar solvent toluene and polar solvents such as dioxane, acetone, and DMF all dramatically reduced the product yields (Table 1, entries 13–16). Additives such as TMEDA and DMEDA also did not result in improved reaction yields (Table 1, entries 17–18).

The promising results prompted us to explore the scope of this new transformation (Table 2). Phenylboronic acids with a methyl group at either the *para*, *meta*, or *ortho* positions reacted smoothly with **1a** in excellent yields (Table 2, entries 1–3). The chloro moiety in 4-chlorophenylboronic acid (**2e**) and the alkoxycarbonyl groups in **1c** and **1d**, which are attached to the phenyl ring bearing the amide group, were well tolerated (Table 2, entries 4, 6, and 7). *N*-Chloro-*N*-phenylbenzamide (**1b**) and heterocyclic type 1-chloro-3,4-dihydroquinolin-2(1H)-one (**1e**) were suitable substrates as well (Table 2, entries 5 and 8). Yet, when alkyl type *N*-butyl-*N*-chlorobutan-1-amine (**1f**) was coupled with **2a** under the current conditions, only 11% of product **3j** was obtained (Table 2, entry 9), and the major components detected were dehalogenated dibutylamine and biphenyl.

Cu-mediated N-arylation of amines or amides with aryl halides as electrophiles have been reported, and they usually required high temperatures.[12–14] In contrast, the reactions described herein proceed smoothly at room temperature. Theoretically, addition of a N–X bond to a low-valent transition metal should be easier than that of a corresponding C–X bond because the former is weaker in strength.[53]

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[*] C. He, C. Chen, J. Cheng, C. Liu, W. Liu, Q. Li, Prof. A. Lei
College of the Chemistry and Molecular Sciences
Wuhan University
Wuhan, Hubei, 430072 (PR China)
Fax: (+86) 27-6875-4067
E-mail: aiwenlei@whu.edu.cn
Homepage: http://www.chem.whu.edu.cn/GCI_WebSite/main.htm

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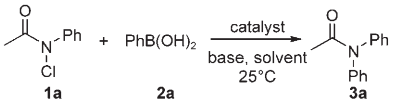
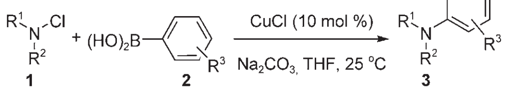
Table 1: Cu-catalyzed N-phenylation of *N*-chloroamide **1a**.[a]

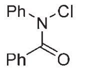
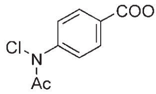
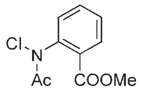
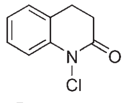
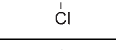


Entry	Catalyst	Base	Solvent	Yield [%][b]
1	CuCl	K_3PO_4	THF	78
2	CuBr	K_3PO_4	THF	65
3	CuI	K_3PO_4	THF	43
4	CuCN	K_3PO_4	THF	<5
5	Cu_2O	K_3PO_4	THF	<5
6	$Cu(OTf)C_6H_6$	K_3PO_4	THF	10
7	$[Cu(CH_3CN)_4]BF_4$	K_3PO_4	THF	<5
8	CuCl	K_2CO_3	THF	52
9	CuCl	Na_2CO_3	THF	99
10	CuCl	Li_2CO_3	THF	28
11	CuCl	KF	THF	22
12	CuCl	CsF	THF	57
13	CuCl	Na_2CO_3	dioxane	35
14	CuCl	Na_2CO_3	toluene	<5
15	CuCl	Na_2CO_3	acetone	<5
16	CuCl	Na_2CO_3	DMF	<5
17[c]	CuCl/TMEDA	Na_2CO_3	THF	22
18[d]	CuCl/DMEDA	Na_2CO_3	THF	53

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), base (3 equiv), copper catalyst (10 mol%) in THF at 25 °C; [b] Yields determined by GC methods; [c] TMEDA (N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine) (10 mol%) was added; [d] DMEDA (N^1,N^2-dimethylethane-1,2-diamine) (10 mol%) was added.

Table 2: CuCl-catalyzed reactions of *N*-chloroamides and arylboronic acids.[a]



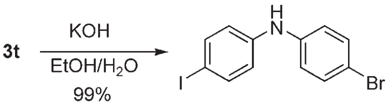
Entry	1		R³	Yield [%][b]
1		**1a**	*o*-Me (**2b**)	96 (**3b**)
2		**1a**	*m*-Me (**2c**)	98 (**3c**)
3		**1a**	*p*-Me (**2d**)	98 (**3d**)
4		**1a**	*p*-Cl (**2e**)	81 (**3e**)
5		**1b**	**2b**	90 (**3f**)
6		**1c**	H (**2a**)	92 (**3g**)
7		**1d**	**2a**	94 (**3h**)
8		**1e**	**2a**	83 (**3i**)
9		**1f**	**2a**	11 (**3j**)

[a] Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), Na_2CO_3 (3 equiv), CuCl (10 mol%) in THF at 25 °C for 36 h. [b] Yields of isolated products.

Therefore, the mild reaction conditions were probably because of the higher reactivity of *N*-chloroamides towards copper catalysts compared to that of aryl halides. Hence, we envisioned that aryl bromide or even aryl iodide moieties could be tolerated under our reaction conditions.

Accordingly, the reaction of **1a** and *p*-bromophenyl boronic acid (**2f**) was tested. To our delight, the desired product was isolated in 88% yield (Table 3, entry 1). Similarly, bromo moieties in the *N*-chloroamide reagent were tolerated; the reactions of **1g** and **1h** with different boronic acids resulted in the desired amides in excellent yields (Table 3, entries 2–6). The reaction was also effective when an iodo moiety was present in the *N*-chloroamides structure; the boronic acids selectively reacted with the N–Cl bond instead of the C–I bond to give the products in yields of 81–99% (Table 3, entries 7–14). Notably, product **3w**, having both a bromo and an iodo substituent at each of the two *ortho* positions was successfully obtained (Table 3, entry 14).

A reaction between 25 g of **1i** and 1.2 equivalents of **2f** was carried out at room temperature with 10 mol% CuCl as the catalyst, and desired product **3t** was isolated in 87% yield.[54] Compound **3t** was then hydrolyzed, and a biarylamine bearing one bromo and one iodo substituent was isolated quantitatively [Eq. (1)].



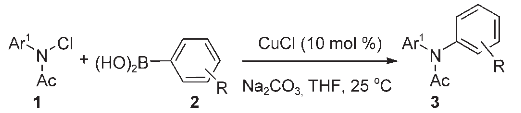
(1)

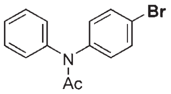
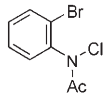
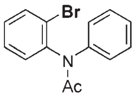
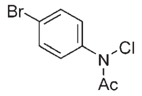
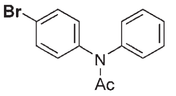
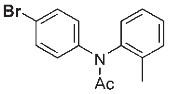
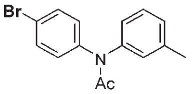
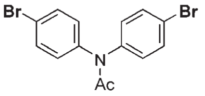
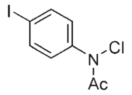
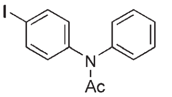
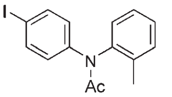
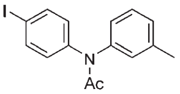
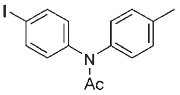
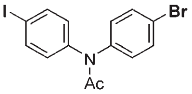
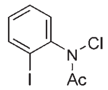
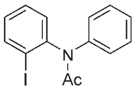
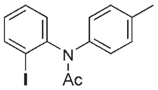
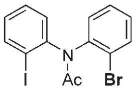
To gain some preliminary understanding of the mechanism, a stoichiometric reaction of ethyl 4-(*N*-chloroacetamido)benzoate (**1c**) with CuCl was monitored in situ by IR methods. Consumption of **1c** and the concomitant formation of a new species were observed. The new species was speculated to be an adduct of **1c** with Cu^I based on the IR spectra (See Figure 1 in the Supporting Information). When the reaction mixture was hydrolyzed, dechlorinated compound ethyl 4-acetamido-benzoate (**4**) was identified by GC analysis, providing evidence of the adduct formation from **1c** and CuCl (See [Eq. (2)] in the Supporting Information).

The proposed catalytic cycle was investigated by running a stoichiometric reaction that was monitored in situ by IR methods. **1c** and 1 equivalent of CuCl were mixed together in THF with subsequent stepwise addition of 1 equivalent of Na_2CO_3 and 1 equivalent of $PhB(OH)_2$ (**2a**). The kinetic profiles (See Figure 2 in the Supporting Information) clearly revealed that **1c** began to react upon the addition of CuCl, and the N-arylation product was formed as soon as the $PhB(OH)_2$ was added. The addition was complete within 5 minutes, and 30% of product **3g** was formed after 360 minutes. Additionally, in the presence of 1 equivalent of a radical scavenger (1,1-diphenylethylene), the catalytic reaction between **1c** and **2a** was not inhibited, and the yield of **3g** was 75% after 300 minutes. Therefore, involvement of radical species in the reaction system was ruled out.

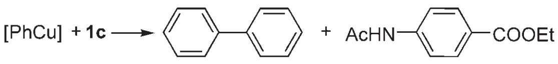
Furthermore, when [PhCu], generated in situ from PhMgCl and CuI, reacted with **1c** at room temperature biphenyl and **4** were the only products obtained, and cross-coupled product **3g** was not detected [Eq. (2)]. This result

Table 3: CuCl-catalyzed reactions of *N*-chloroamides and arylboronic acids bearing halo substituents.[a]



Entry	1		R	3		Yield [%][b]
1		**1a**	*p*-Br (**2f**)		**3k**	88
2		**1g**	**2a**		**3l**	92
3		**1h**	**2a**		**3k**	99
4		**1h**	**2b**		**3m**	97
5		**1h**	**2c**		**3n**	99
6		**1h**	**2f**		**3o**	84
7		**1i**	**2a**		**3p**	91
8		**1i**	**2b**		**3q**	99
9		**1i**	**2c**		**3r**	99
10		**1i**	**2d**		**3s**	95
11		**1i**	**2f**		**3t**	87
12		**1j**	**2a**		**3u**	99
13		**1j**	**2d**		**3v**	99
14		**1j**	*o*-Br (**2g**)		**3w**	81

[a] Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), Na_2CO_3 (3 equiv), CuCl (10 mol %) in THF at 25 °C for 36 h; [b] Yields of isolated products.



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(2)

indicated that transmetalation of the arylboronic acid before introduction of the amide group to the copper center was not a favorable route in this system. Therefore, all the above preliminary examinations provided evidence to support the speculation that the reaction of *N*-chloroamide and copper catalyst was the first step in the catalytic cycle (Scheme 1).

In conclusion, we have utilized easily prepared and highly reactive *N*-chloroamides to develop an efficient copper-catalyzed electrophilic amination of arylboronic acids. The transformation proceeded in high yields to form diarylamides and tolerated a wide variety of functional groups, including iodo, bromo, and chloro moieties, which are typically sensitive in palladium-catalyzed reactions.[55] A scale up experiment was carried out to show the practicability of the method to provide biaryl amides or amines having sensitive substituents. The availability of various boronic acids promises highlights the potential of the methodology. Preliminary mechanistic studies support the proposed mechanism and the results of additional investigations that are ongoing in our laboratory will be reported in due course.

Experimental Section

General procedure for the amination of arylboronic acids by *N*-chloroamides: *N*-chloroamide **1i** (1.0 mmol), arylboronic acid **2f** (0.5 mmol), CuCl (0.05 mmol), and Na_2CO_3 (1.5 mmol) were added to an oven-dried Schlenk tube. The tube was evacuated and refilled with nitrogen three times, and then dry THF (1.5 mL) was added by syringe. The resulting suspension was stirred for 36 h at room temperature and then quenched with 1 mL saturated sodium hyposulfite aqueous solution and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined and dried over sodium sulfate. Pure product was obtained after silica gel chromatography of the crude mixture. The yield of the isolated product was 87 %. *N*-(4-bromophenyl)-*N*-(4-iodophenyl)acetamide (**3t**) ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$–7.68 (m, 2H), 7.50–7.48 (m, 2H), 7.12 (d, $J = 7.8$, 2H), 6.99 (d, $J = 7.8$, 2H), 2.04 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.6$, 140.0, 139.3, 136.3, 130.3, 127.2, 126.3, 21.6 ppm; HRMS (ESI) calcd for $C_{14}H_{11}BrINO$ $[M+H]^+$: 415.9147; found: 415.9139.

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Keywords: amides · amination · copper · cross-coupling · homogeneous catalysis

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[54] The excess of *N*-haloamides to arylboronic acids was to improve the conversion of arylboronic acids. The side products detected were mainly dechlorinated amides. The screening experiments (see the Supporting Information) revealed that when the ratio between **2a** and **1c** was lowered to 1.3:1, the yield decreased by about 10%.
[55] Our method has been compared with the Cu^{II}-mediated oxidative coupling (Chan–Lam–Evans procedure and one of modified procedures), and the yields of the latter were lower (see the Supporting Information).