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Copper-Catalyzed Carbonylative Cross-Coupling of Arylboronic Acids with *N*-Chloroamines to Synthesis Aryl Amides

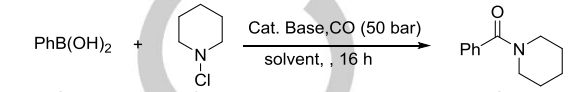
Zhiping Yin,[a] Zechao Wang,[a] Wanfang Li[a] and Xiao-Feng Wu*[a,b]

Abstract: A novel copper-catalyzed carbonylative cross-coupling between *N*-chloroamines and arylboronics acids has been developed. With copper(I) oxide as the catalyst, various the desired amide compounds were produced in moderate to good yields. Functional groups such as iodide and alkene can be tolerated. Notably, this is the first example on copper-catalyzed aminocarbonylation of *N*-chloroamines.

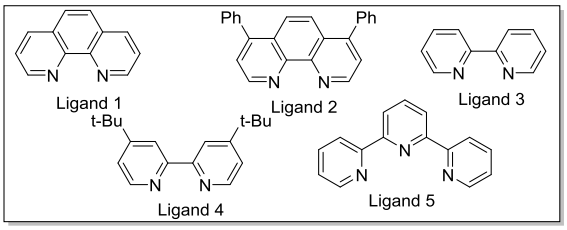
Amide is one of the most important function groups in chemistry, it presents in proteins and also found wildly in numerous natural products and pharmaceutical molecules.[1] Although their obvious importance, the most commonly applied method for their construction is based on the combination of activated carboxylic acids derivatives and amines. Although a vast amount of efforts have been devoted to develop more efficient methodologies for amides synthesis, drawbacks including the usage of expensive reagents, low functional group tolerance and low reaction efficiency are remaining.[2] Therefore, the developments of new and more efficient methods for amides synthesis are still under current request.[3,4]

On the other hand, transition metal-catalyzed carbonylative coupling reactions have already become a powerful toolbox in modern organic synthesis. Various carbonyl-containing molecules can be effectively produced by introducing carbon monoxide into the parent compounds. Depending on the nucleophiles applied, aminocarbonylation, with amines as the coupling partner, provides a promising pathway for amides preparation.[5] However, most of the developed procedures are facing two challenges: using aryl halides as the electrophiles and using palladium as the catalysts.[6] Under these backgrounds and also from the academic point of view, we feel it will be attractive to apply *N*-chloroamine as reagent in the carbonylative synthesis of amides which have reported in cross-coupling reactions.[7] Additionally, due to the advantages of copper salts compared with noble metal catalysts, we decided to explore the possibility of applying copper catalysts in carbonylative coupling transformations.[8]

Table 1. Optimization of the reaction conditions.[a]



Entry	Base	Cat. (X mol%)	Solvent	T °C	Yield (%)[b]
1	$NaHCO_3$	Cu_2O (10)	MTBE	40 °C	50[c]
2	$NaHCO_3$	Cu_2O (10)	MTBE	50 °C	63[c]
3	$NaHCO_3$	Cu_2O (10)	MTBE	25 °C	35
4	$NaHCO_3$	CuBr•Me_2S (10)	MTBE	50 °C	58
5	$NaHCO_3$	$Cu(acac)_2$ (10)	MTBE	50 °C	28
6	$NaHCO_3$	$Cu(OSO_2CF_3)$ (10)	MTBE	50 °C	35
7	$NaHCO_3$	$Cu(MeCN)_4$•BF_4 (10)	MTBE	50 °C	33
8	$NaHCO_3$	CuBr(Ligand 1)PPh_3 (10)	MTBE	50 °C	23
9	$NaHCO_3$	CuCl(iPr) (10)	MTBE	50 °C	14
10	$NaHCO_3$	Cu_2O+Ligand 1 (10)	MTBE	50 °C	11
11	$NaHCO_3$	Cu_2O+Ligand 2 (10)	MTBE	50 °C	29
12	$NaHCO_3$	Cu_2O+Ligand 3 (10)	MTBE	50 °C	62
13	$NaHCO_3$	Cu_2O+Ligand 4 (10)	MTBE	50 °C	10
14	$NaHCO_3$	Cu_2O+Ligand 5 (10)	MTBE	50 °C	3
15	tBuOLi	Cu_2O (10)	MTBE	50 °C	6
16	tBuOK	Cu_2O (10)	MTBE	50 °C	0
17	PhONa	Cu_2O (10)	MTBE	50 °C	0
18	$NaHCO_3$	Cu_2O (10)	DCE	50 °C	3
19	$NaHCO_3$	Cu_2O (10)	Benzene	50 °C	4
20	**$NaHCO_3$**	**Cu_2O (5)**	**MTBE**	**50 °C**	**69 (66)[c]**
21	$NaHCO_3$	Cu_2O (20)	MTBE	50 °C	60



[a] Conditions (unless otherwise stated): **1a** (0.25 mmol), **2a** (0.5 mmol) ,Base (0.75 mmol), solvent 2 mL, 50 °C, CO (50 bar), 16 h. [b] GC yields were determined by using hexadecane as the internal standard. [c] isolated yield. DCE = 1,2-dichloroethane; MTBE = methyl *tert*-butyl ether. iPr = 1.3-bis(2.6-diisopropylphenyl)imidazol-2-ylidene.

Initially, the reaction was performed using copper oxide, $NaHCO_3$, $PhB(OH)_2$ in MTBE under pressure of CO (50 bar) at 40**°**C. To our delight, the desired product was obtained with 50% isolated yield (Table 1, entry 1). And the yield can be further improved to 63% **BY** rising the reaction temperature to 50 **°C** (Table 1, entry 2)**.** Then we continued to optimize the reaction condition and a series of copper catalysts were evaluated, including CuBr(Me_2S), $Cu(acac)_2$, $Cu(OSO_2CF_3)$, $Cu(MeCN)_4{\cdot}BF_4$, CuBr(ligand 1)PPh_3 and CuCl(iPr) (Table 1, entries 4-9). But all this copper catalysts were inferior to Cu_2O.

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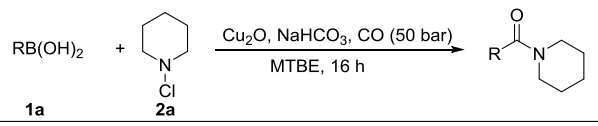
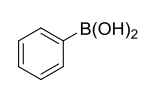
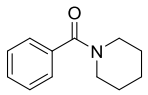
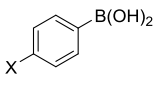
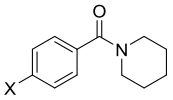
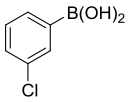
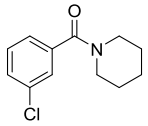
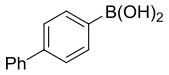
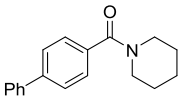
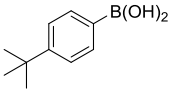
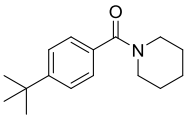
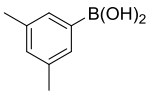
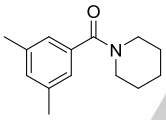
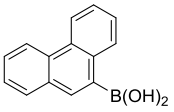
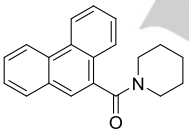
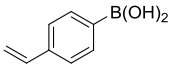
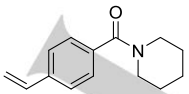
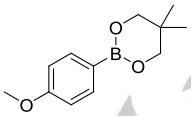
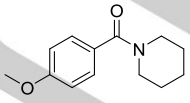
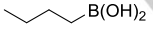
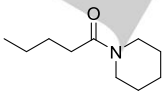
Table 2. Cu-catalyzed aminocarbonylation of *N*-chloroamines: Scope of arylboronic acids.[a]



1a **2a**

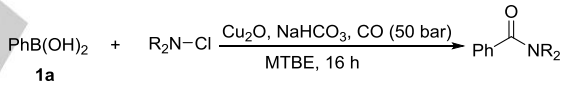
Entry	Substrate	Product	yield[b]
1			66%
2 3 4			X = F 63% X = Br 60% X = I 69%
5			53%
6			64%
7			69%
8			76%
9			71%
10			23%
11			18%
12			0%

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol) , Cu_2O (5 mol%), $NaHCO_3$ (0.75 mmol), MTBE (2 mL), 50 °C, CO (50 bar), 16 h. [b] Isolated yields.

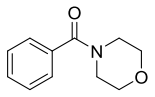
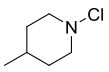
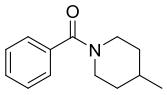
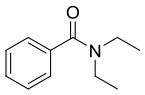
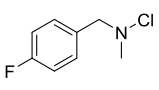
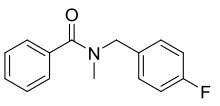
Subsequently, nitrogen ligands were tested with Cu_2O (Table 1, entries 10-14). However, no positive effect could be observed with the tested ligands. Successively, different bases and solvents were studied. When tBuOLi or PhONa tested as the base, no desired product could be detected (Table 1, entries 16 and 17) and only 6% yield was obtained with tBuOK as base (Table 1, entry 15). Furthermore, the reaction efficiency dropped dramatically when using DCE or Benzene as the reaction media (Table 1, entries 18 and 19). The loading of Cu_2O was checked as well (Table 1, entries 20-21). The amount of catalyst can be decreased to 5 mol% without losing reaction efficiency. Finally, we found that the combination of 5 mol% Cu_2O and $NaHCO_3$ (1.5 equiv.) under CO atmosphere (50 bar) at 50**°C** for 16 h provide the best outcome of target product (66%; Table 1, entry 20).

With the optimized reaction conditions in hand, we examined the substrates scope of this transformation with a range of boronic acids. As shown in Table 2, the desired amide products were formed in good yields in general with the arylboronic acids tested with 1-chloropiperidine. Halogen functional groups can be well tolerated, moderate to good yields of the desired amides were isolated (Table 2, entries 2-5). Notably, 69% of (4-iodophenyl)(piperidin-1-yl)methanone was produced successfully under our conditions (Table 2, entry 4). The other alkyl and aryl substituted arylboronic acids can be applied as well and provide the desired amides in good yields (Table 2, entries 6-9). However, when using (4-vinylphenyl)boronic acid or 2-(4-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane as the starting materials, the yield of the desired products drops dramatically (Table 2, entries 10 and 11). And no desired product could be detected with alkylboronic acid (Table 2, entry 12). Additionally, no reaction occurred with $PhBF_3K$ and 4-methoxyphenylboronic acid, but the decomposition of the substrates.

Table 3. Cu-catalyzed aminocarbonylation of *N*-chloroamines: Scope of chloroamines.[a]



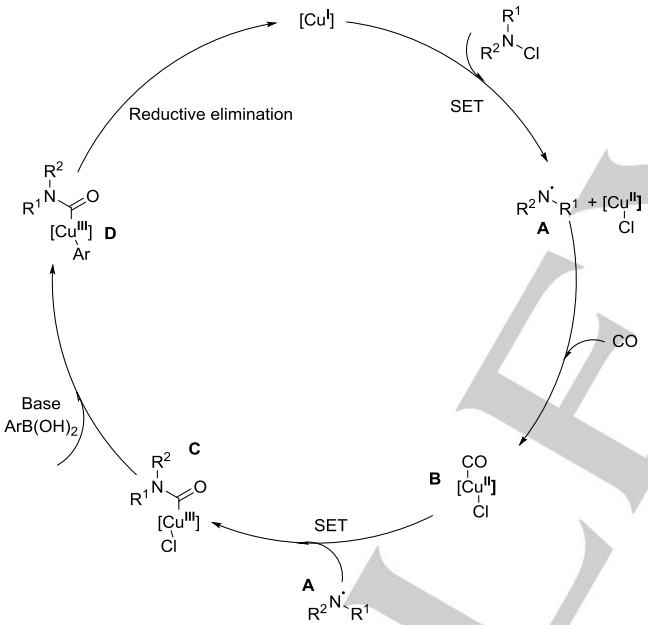
1a

Entry	Substrate	Product	yield[b]
1			48%
2			51%
3[b]			22%
4			45%

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol) , Cu_2O (5 mmol%), $NaHCO_3$ (0.75 mmol), MTBE (2 mL), 50 °C, CO (50 bar), 16 h. [b] **1a** (0.25 mmol), **2a** (0.5 mmol) , Cu_2O (5 mmol%), NCS (0.55 mmol), diethylamine (0.5 mmol), $NaHCO_3$ (0.75 mmol), MTBE (2 mL), 50 °C, CO (50 bar), 16 h. [b] Isolated yields .

Furthermore, various *N*-chloroamines were prepared and tested under our reaction conditions.[9] As shown in Table 3, moderate yields can be observed from the reaction of 4-chloromorpholine, 1-chloro-4-methylpiperidine and *N*-chloro-1-(4-fluorophenyl)-*N*-methylmethanamine with phenylboronic acid under identical conditions. Notably, the attempting in using of primary amines and aromatic amines analogues of chloroamines as substrates were all failed, either substrates decomposition or the corresponding ureas were detected.

Based on our results and literature, a possible reaction mechanism is proposed (Scheme 1).[7j] Firstly, dialkylaminyl radical **A** is generated by SET process from the *N*-choro dialkylamine and the Cu(I) is been oxidized to Cu(II). Under CO pressure, CO coordinated with Cu(II) to give the intermediate **B**. Then intermediate **C** was formed from the reaction of dialkylaminyl radical and Cu(II) **B**. The carbmoyl-metal intermediate **C** undergoes transmetalation with boronic acid to form the intermediate **D**, which then affords the final amide product after reductive elimination while the active Cu (I) species is regenerated for the next catalytic cycle.



Scheme 1. Proposed reaction mechanism.

In summary, a copper-catalyzed aminocarbonylation reaction of *N*-chorolamines with boronic acids has been developed. With Cu_2O as the catalyst, a series of aromatic amides were synthesized in moderate to good yields from the corresponding substrates. Notably, this is the first example on copper-catalyzed aminocarbonylation of *N*-chloroamines.

Experimental Section

To each screw-cap vial (4 ml) equipped with a septum, a small cannula, and a stirring bar was added with boronic acid (0.25 mmol), $NaHCO_3$ (63 mg, 0.75 mmol) and Cu_2O (1.8 mg, 0.013 mmol). The vials then were then purged with argon three times before the *N*-chloroamines (0.5 mmol) and tBuOMe (2 mL) were added to the reaction mixture by springe. The vials were then placed on an alloy plate and transferred into a 300 ml autoclave of the 4560 series from Parr instruments under air. After flushing the autoclave three times with CO, a pressure of 50 bar CO was settled and the reaction was performed for 16 hours at 50°C. Afterwards, the autoclave was cooled to room temperature and the pressure was released carefully. The solvent was removed under reduced pressure and the crude products were purified by column chromatography on silica gel (eluent: pentane/ethyl acetate = 3:1)

Acknowledgements

The analytic supports of Dr. W. Baumann, Dr. C. Fisher, S. Buchholz, and S. Schareina are gratefully acknowledged. We also appreciate the general supports from Professor Matthias Beller and Professor Armin Börner in LIKAT.

Keywords: copper catalyst • carbonylation • amide • radical • *N*-chloroamines

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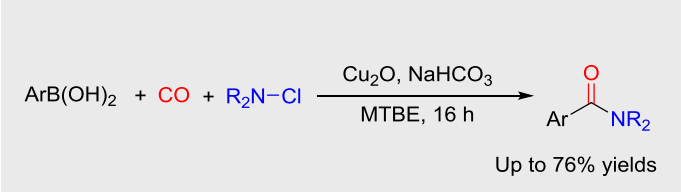

Corp(Copper) CO! A novel copper-catalyzed carbonylative cross-coupling between *N*-chloroamines and arylboronics acids has been developed. With copper(I) oxide as the catalyst, various the desired amide compounds were produced in moderate to good yields.

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Copper-Catalyzed Carbonylative Cross-Coupling of Arylboronic Acids with *N*-Chloroamines to Synthesis Aryl Amides