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$Cu(BF_4)_2$/AC-Catalyzed Synthesis of *N*-Substituted Anilines, *N*-Substituted 1,6-Naphthyridin-5(6*H*)-one, and Isoquinolin-1(2*H*)-one

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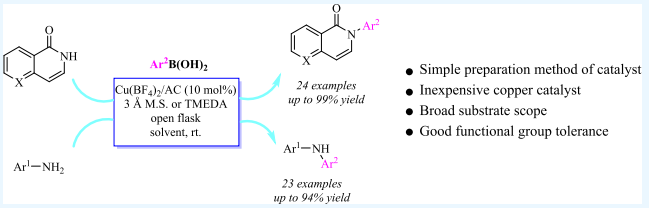
ABSTRACT: Herein, we report practical $Cu(BF_4)_2$/activated carbon-catalyzed amination of various anilines, isoquinolinone, and naphthyridinone with aryl boronic acids. The ultrasonic and rotary evaporation treatment of the mixture of aq. $Cu(BF_4)_2$ and activated carbon in methanol afforded a novel Cu(II)-catalyst, which is air-stable and can be effectively applied in the Chan–Lam coupling reaction. The products of *N*-arylation were isolated in good to excellent yields at low catalytic loading. And $Cu(BF_4)_2$/AC also showed good reusability.



INTRODUCTION

Substituted isoquinolinones and naphthyridinones form an important class of compounds in the pharmaceutical industry.[1,2] Particularly, substituted isoquinolin-1(2*H*)-one, which constitutes the core scaffold of marketed or reported small molecular inhibitors, such as Duvelisib, compound **4**, and Eganelisib, made this heterocycle a popular pharmacophore for synthetic chemists (Scheme 1, compounds **1**, **3**, and **4**).[3−5] Naphthyridinone also acted as a small molecular inhibitor against some medicinal targets (compounds **2**, **5**, **6**).[6−8] The Ullmann coupling reaction or multistep cyclization are commonly used to construct *N*-phenyl-isoquinolinone segments.[9,10] However, these suffer from several limitations, such as expensive copper salts, air-sensitive ligands, and harsh reaction conditions, thus hampering the application of conventional synthetic methods.[11]

Although the Buchwald–Hartwig coupling is another well-known C–N bond formation method and is dramatically used in synthetic chemistry,[12,13] some drawbacks still restrict its wide application.[14] Since its first discovery in 1998, the Chan–Lam amination methodology has emerged as one of the three most prominent cross-coupling reactions for the formation of the C–N bond. This route uses the aryl organoboron derivatives to react with nucleophiles under facile reaction conditions (open flask or O_2 balloon, room temperature, weak base).[15,16] Compared to the routinely exploited Ullmann and Buchwald–Hartwig coupling, the Chan–Lam amination was a more practical method to construct the C–N bond.

Aryl boronic acids served as an acceptor and were widely applied in Chan–Lam coupling, which has been extensively studied in mechanistic description:[17] (1) A weak base or an essential additive always played an important role in the process of deprotonation in the reaction. (2) Different copper salts work differently in the presence of various additives. (3) Small amounts of H_2O in the solvent might facilitate the coupling reaction. Many modifications have been reported to improve the reaction efficiency using different copper salts, such as $Cu(OAc)_2$, CuOAc, CuCl, $Cu(OTf)_2$, and $[Cu(OH)\cdot TMEDA]_2Cl_2$.[18−21] However, apart from its application in oxidative C–C coupling with pyrene derivatives, $Cu(BF_4)_2\cdot nH_2O$-mediated C–N formation has rarely been explored (Scheme 2a).[22] Its high hygroscopicity maybe restrict the applications.[23]

Several heterogeneous copper catalysts have been prepared to expand the scope of substrates and improve the efficiency of the Chan–Lam reaction (Scheme 2b). For example, Kantam reported copper fluorapatite (CuFAP) facile-catalyzed *N*-arylation of imidazole and anilines at room temperature.[24] Beletskaya designed copper nanoparticles supported on zeolite to catalyze the formation of C–C, C–S, and C–N bonds.[25] Thereafter, various heterogeneous catalyst systems were disclosed, such as $CuSO_4/Fe_3O_4$-EDTA,[26] $Cu(OAc)_2$/graphene oxide,[27] $Cu(OAc)_2$/MCIP-1,[28] and Cu (II)/chitosan,[29] etc. But these reported methods still suffered from some drawbacks, such as large catalyst usage, expensive ligands or base, substrate specificity, complex post-processing, and side products.[30] Therefore, the development of an efficient, economical, and environmental-friendly catalyst system for the Chan–Lam coupling reaction has drawn promising interest.

Activated carbon-supported transition metal catalysts, such as Pd/AC, Pt/AC, and Co/AC, have been widely used in

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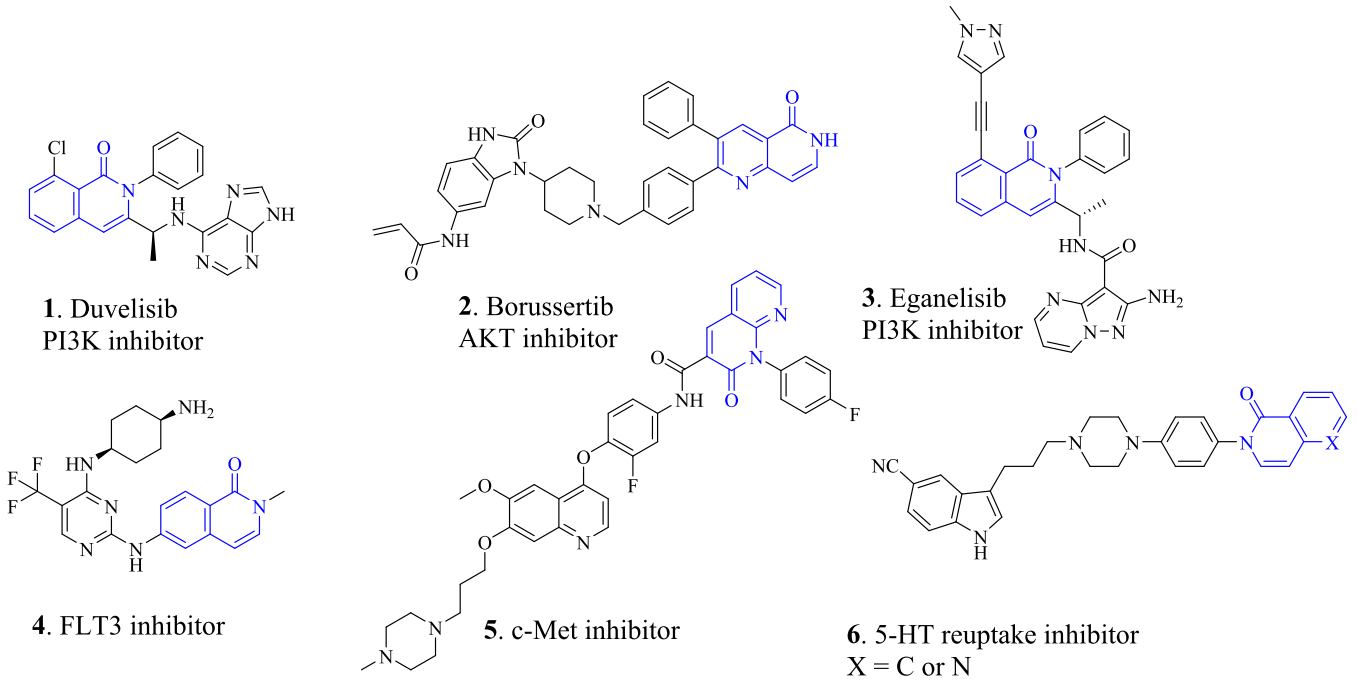
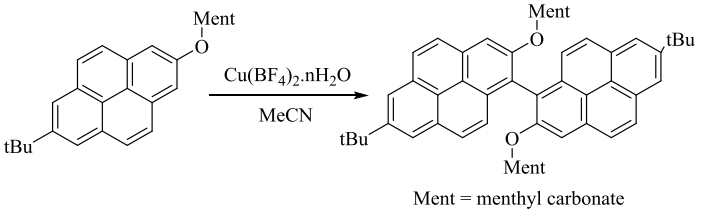
Scheme 1. Chemical Structures of Reported Isoquinolinone or Naphthyridinone-Based Inhibitors

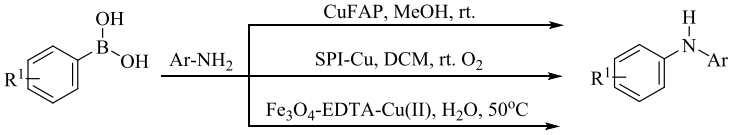


Scheme 2. $Cu(BF_4)_2{\cdot}nH_2O$ Catalyzed Oxidative C−C Coupling Reaction and Copper-Catalyzed C−N Bond Formation

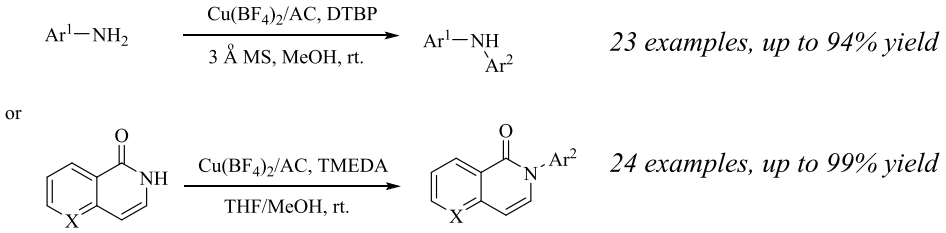
a. Previous reports: $Cu(BF_4)_2.nH_2O$ catalyzed oxidative coupling reaction



b. Previous reports: Copper catalyzed Chan-Lam coupling



c. This work: the discovery and application of heterogeneous catalyst systems of $Cu(BF_4)_2$/AC



numerous organic transformations.[31−33] However, Cu(II)/AC catalysts have not been well utilized in the industry. Herein, an effective, easy-prepared, and economical activated carbon-supported $Cu(BF_4)_2$ catalyst was developed for efficient amination of anilines, isoquinolin-1(2*H*)-one, and 1,6-naphthyridin-5(6*H*)-one with aryl boronic acids (Scheme 2c).

EXPERIMENTAL SECTION

Materials and Methods. Unless otherwise noted, all starting materials, reagents, and solvents were commercially available and used without further purification. The intermediates and end-products were purified by flash column chromatography with silica gel 60 (200−300 mesh). Chemical

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reactions were monitored by thin-layer chromatography (TLC) or liquid chromatography (LC)/mass spectrometry (MS). LC/MS was performed on an Agilent HPLC1260-MS6120 system (column: Agilent-SB-C18, 2.5 mm × 30 mm, 3.5 μm). ^{1}H NMR and ^{13}C NMR spectra were obtained using $CDCl_3$ or DMSO-d_6 as a solvent on a Bruker Avance III 400 or 600 M frequency spectrometer. The coupling constant J is given in hertz. NMR data are reported as follows: chemical shift (TMS as an internal standard), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet, dt = double triplet), coupling constants, and integration. Specific surface areas were calculated using Brunauer–Emmett–Teller (BET) theory. Scanning electron microscopy (SEM) was performed on a field emission Hitachi SU8220 electron microscope. X-ray diffraction (XRD) patterns were collected using a Bruker D8 Advance X-ray powder diffractometer (Cu Kα1) over a 2θ range of 5–60 with Bragg–Brentano geometry. For X-ray photoelectron spectroscopy (XPS), the sample was pressed onto indium foil and monitored on a Thermo Fisher Scientific K-α X-ray photoelectron spectrometer.

Preparation of the $Cu(BF_4)_2$/AC Heterogeneous Catalyst. Commercially available 45 wt % aq. $Cu(BF_4)_2$ solution (1.0 g) was added to a mixed solution of methanol (50 mL) and dichloromethane (100 mL). Subsequently, active carbon (5.0 g) was added to the mixture. The ultrasonic (5 min) and rotary evaporation treatment of the mixture solution gave a black powder $Cu(BF_4)_2$/AC (5.8 g, 7.7 mass %).

Typical Procedure for Preparing 3a-m by *N*-Arylation of Aniline with Substituted Phenylboronic Acid. In a typical experimental procedure, di-*tert*-butyl peroxide (2.0 mmol) was dropwise added to a mixture of aniline (1.0 mmol), $Cu(BF_4)_2$/AC (10 mol %), 3 Å. MS (1.2 g), and substituted phenylboronic acid (2.5 mmol) in methanol (2 mL) at room temperature, and the mixture was stirred for 12 h. After TLC showed the disappearance of the starting material disappeared, the reaction mixture was filtered and the filtrate was concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography on silica gel (eluent:ethyl acetate/petroleum ether = 0–1/1) to afford the *N*-phenylaniline derivatives **3a-m**.

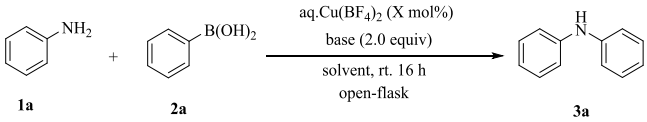
Typical Procedure for Preparing 3n-s, 3g-h, and 3k-l by *N*-Arylation of Substituted Aniline with Phenylboronic Acid. In a typical experimental procedure, di-*tert*-butyl peroxide (2.0 mmol) was dropwise added to a mixture of substituted aniline (1.0 mmol), $Cu(BF_4)_2$/AC (10 mol %), 3 Å. MS (1.2 g), and phenylboronic acid (2.5 mmol) in methanol (2 mL) at room temperature, and the mixture was stirred for 12 h. After TLC showed the disappearance of the starting material, the reaction mixture was filtered and the filtrate was concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography on silica gel (eluent:ethyl acetate/petroleum ether = 0–1/1) to afford the *N*-phenylaniline derivatives **3n-s, 3g-h, and 3k-l**.

Typical Procedure for Preparing 6a-x by *N*-Arylation of Isoquinolin-1(2*H*)-one and 1,6-Naphthyridin-5(6*H*)-one with Various Substituted Phenylboronic Acids. In a typical experimental procedure, $Cu(BF_4)_2$/AC (10 mol %) was added to a mixture of isoquinolinone or naphthyridinone (1.0 mmol), TMEDA (3.0 mmol), and aryl boronic acid (2.5 mmol) in a mixed solvent (10.0 mL, THF/MeOH = 4.0/6.0 mL) at room temperature and the mixture was stirred until no starting material was detected by TLC. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography on silica gel with an eluent (ethyl acetate /petroleum ether = 0–3/1) to afford the desired product **6a-x**.

RESULTS AND DISCUSSION

To gain an optimized protocol for the synthesis of *N*-phenylaniline, we initiated our studies on phenylamine (**1a**) and phenylboronic acid (**2a**) in the presence of different doses of aq. $Cu(BF_4)_2$ (45 wt % in water). As shown in Table 1, when 3% of the copper salt was applied, only 41% product was performed (entry 1). A moderately increased yield was observed after increased usage of the copper salt (entry 2). Lastly, a stoichiometric amount of catalyst (entry 3) led to the formation of **3a** in an 87% yield. Subsequently, we carefully optimized the solvent and base in the presence of 10% copper salt. Relatively, MeOH, EtOAc, and 1,4-dioxane were preferable (entries 4–8). In contrast, TMEDA was a better organic base choice (entry 9 vs 12; Table S1, entry 3). Compared to TMEDA or K_2CO_3, the strong basicity of DBU or KOH did not indicate the benefits (entries 10 and 11). All of these indicated that TMEDA and K_2CO_3 both appeared to be the optimized bases for efficient reactivity. And these data also demonstrated that aq. $Cu(BF_4)_2$ could be used as a moderately effective catalyst for Chan–Lam coupling.

Table 1. Screening Reaction Conditions[a]



1a 2a 3a

entry	X	atm.	base	solvent	yield[d]
1	3	air	K_2CO_3	1,4-dioxane	41%
2	10	air	K_2CO_3	1,4-dioxane	62%
3	100	air	K_2CO_3	1,4-dioxane	87%
4	10	air	K_2CO_3	*tert*-butanol	4%
5	10	air	K_2CO_3	MeOH	59%
6	10	air	K_2CO_3	THF	51%
7	10	air	K_2CO_3	EtOAc	65%
8	10	air	K_2CO_3	DCM	14%
9	10	air	TMEDA	1,4-dioxane	67%
10	10	air	DBU	1,4-dioxane	19%
11	10	air	KOH	1,4-dioxane	14%
12	10	air	DIPEA	1,4-dioxane	12%
13	10	N_2	K_2CO_3	1,4-dioxane	NR
14	10[b]	air	K_2CO_3	1,4-dioxane	82%
15	10[c]	air	K_2CO_3	1,4-dioxane	80%

[a]Unless otherwise noted, all of the reactions were run with **1a** (2.1 mmol), **2a** (2.5 equiv), and base (2.0 equiv) under air in 10.0 mL of solvent. Equivalents (equiv) refer to the mole ratio to aniline. [b]Content value of $Cu(BF_4)_2$/AC was 7.7 mass %. [c]Content value of $Cu(BF_4)_2$/AC was 15.4 mass %. [d]Isolated yields.

During the reaction proceeding, the addition of phenylboronic acid in a ratio of 1:1.5 to 1:3 (**1a**: **2a**) did not afford improvement in the yield (Table S1, entries 1–4). The reason for this phenomenon is the formation of several byproducts, such as azobenzene, phenol, and diphenyl ether, which could inversely be heightened by H_2O in the catalyst or atmosphere (Scheme 3). On this basis, to eliminate the influence of H_2O, a heterogeneous catalyst system containing activated carbon and $Cu(BF_4)_2$ was subsequently prepared. And with a lower catalyst

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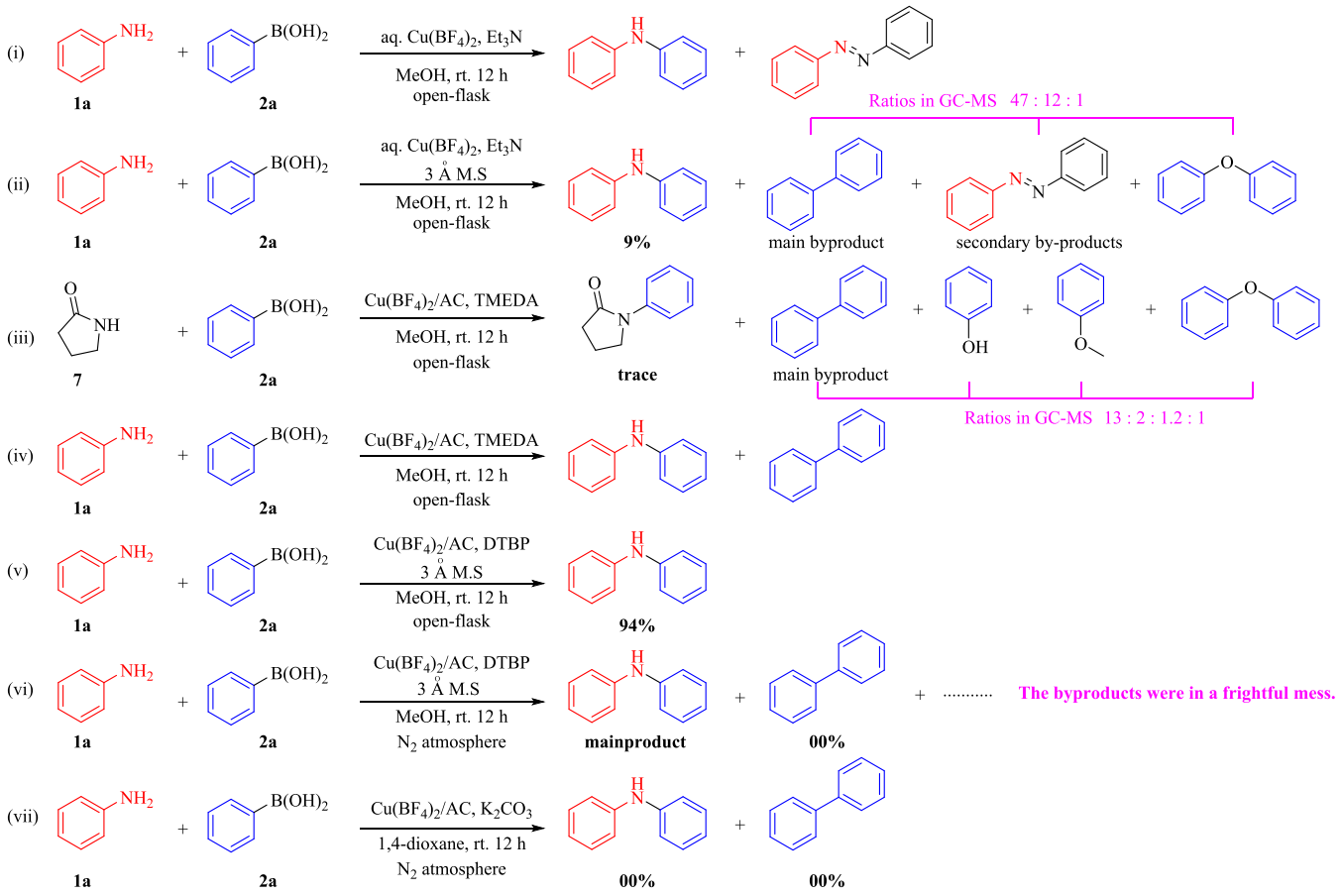
Scheme 3. Control Experiments



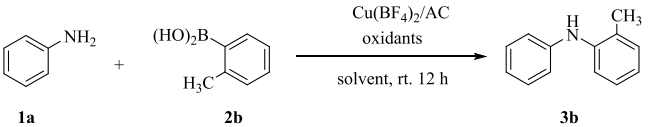
content, a slightly higher yield of 82% was obtained (entries 14 and 15) with no open flask and no diphenylamine (entry 13).

In expanding the substrate range, employing methyl, ethyl, or bromo atom as the *ortho*-substituent in phenylboronic acid, its reaction resulted in low yields (Table S2, **3b**, **3c**, **3i**, 38, 27, 28%). The phenylation of 2-fluoroaniline showed a trace product. And the formation of 1-phenyl-3,4-dihydroquinolin-2(1*H*)-one was found to be in a moderate yield (Table 4, **6w**, 34%). In addition, using TMEDA as a base, *N*-phenylation of 1,6-naphthyridin-5(6*H*)-one showed good reactivity with an excellent yield of 99% (Table S3, **6m**). The changes in the yield of benzamide derivatives may be due to the nucleophilicity of abundant NH-amides. Therefore, we knew that the $Cu(BF_4)_2$/AC catalytic system could not be further applied to the *N*-arylation of *o*-substituent anilines unless a big change was made.

Normally, oxygen (O_2) is considered an economic and environmentally friendly oxidant for Chan−Lam coupling. As shown in Table 2, the O_2 balloon did slightly increase the yield to 41% (entries 1 and 2). Using di-*tert*-butyl peroxide (DTBP), a significant increase in yield was observed even in the absence of a base (entry 3). Compared with 1,4-dioxane, the coupling reaction was carried out with higher efficiency in methanol in the presence of molecular sieves (entries 4 and 5). This might be due to the higher solubility of *ortho*-tolylboronic acid in methanol.

With the optimized conditions and oxidant in hand, we examined the substrate scope of the $Cu(BF_4)_2$/AC-catalyzed Chan−Lam coupling reaction between phenylamines with phenylboronic acids under open-flask conditions. These results are summarized in Table 3. All products were obtained as yellow

Table 2. Conditions Screening of the $Cu(BF_4)_2$/AC-Catalyzed Oxidative Coupling Reaction of Phenylamine with *ortho*-Tolylboronic Acid[a]



1a 2b 3b

entry	oxidant[b]	additive[c]	solvent[d]	yield (%)
1	air	K_2CO_3	1,4-dioxane	38
2	O_2	K_2CO_3	1,4-dioxane	41
3	DTBP	no base	1,4-dioxane	57
4	DTBP	M.s. 3 Å	1,4-dioxane	58
5	DTBP	M.s. 3 Å	methanol	93

[a]Unless otherwise noted, all of the reactions were run with **1a** (1.0 mmol), **2b** (2.5 mmol). [b]Reaction performed using DTBP (2.0 mmol), O_2 balloon, air = open flask. [c]K_2CO_3 (2.0 mmol). [d]1,4-Dioxane (10.0 mL), methanol (2.0 mL).

or colorless oil and characterized by ^1H NMR, ^{13}C NMR, and mass spectra.

All *ortho*-alkyl on the aryl boronic acid provided the corresponding diphenylamine derivatives in excellent yields. The amination of phenylamine (**1a**) with *ortho*/*para*-tolyl phenylboronic acid (**2b**, **2g**) gave yields similar to phenylboronic acid (entries 1, 2, and 7). The reaction of 2-ethylphenylboronic acid (**2c**) with aniline gave **3c** in a lower yield (79%) than **3b** (entry 3). However, when methyl was located in the *meta*-position, the yield of **3f** dropped slightly to

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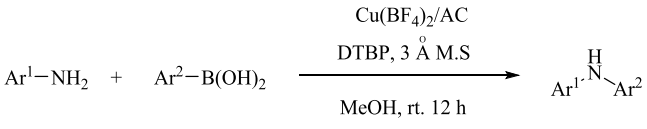
Table 3. Investigation of the Scope of Substituted Phenylboronic Acids and Aniline Derivatives[a]



1 2 3

entry	Ar^1	Ar^2	Pd.	yield (%)[b]
1	phenyl (**1a**)	phenyl (**2a**)	**3a**	94
2	phenyl (**1a**)	2-Me-C_6H_4 (**2b**)	**3b**	93
3	phenyl (**1a**)	2-Et-C_6H_4 (**2c**)	**3c**	79
4	phenyl (**1a**)	2,6-*di*-Me-C_6H_4 (**2d**)	**3d**	52
5	phenyl (**1a**)	3,5-*di*-Me-C_6H_4 (**2e**)	**3e**	72
6	phenyl (**1a**)	3-Me-C_6H_4 (**2f**)	**3f**	82
7	phenyl (**1a**)	4-Me-C_6H_4 (**2g**)	**3g**	96
8	phenyl (**1a**)	2-F-C_6H_4 (**2h**)	**3h**	24
9	phenyl (**1a**)	2-Br-C_6H_4 (**2i**)	**3i**	43
10	phenyl (**1a**)	4-F-C_6H_4 (**2j**)	**3j**	85
11	phenyl (**1a**)	4-Cl-C_6H_4 (**2k**)	**3k**	76
12	phenyl (**1a**)	3-NO_2-C_6H_4 (**2l**)	**3l**	80
13	phenyl (**1a**)	3-MF-C_6H_4 (**2m**)	**3m**	94
14	4-NO_2-C_6H_4 (**1n**)	phenyl (**2a**)	**3n**	74
15	4-Br-C_6H_4 (**1o**)	phenyl (**2a**)	**3o**	85
16	4-*tert*-butyl-C_6H_4 (**1p**)	phenyl (**2a**)	**3p**	86
17	4-CF_3-C_6H_4 (**1q**)	phenyl (**2a**)	**3q**	59
18	3-Br-4-Cl-C_6H_4 (**1r**)	phenyl (**2a**)	**3r**	68
19	4-Me-C_6H_4 (**1g**)	phenyl (**2a**)	**3g**	86
20	4-Cl-C_6H_4 (**1k**)	phenyl (**2a**)	**3k**	80
21	2-F-C_6H_4 (**1h**)	phenyl (**2a**)	**3h**	62
22	3-NO_2-C_6H_4 (**1l**)	phenyl (**2a**)	**3l**	83
23	4-piperidin-C_6H_4(**1s**)	phenyl (**2a**)	**3s**	75

[a]Unless otherwise noted, all of the reactions were run with **1** (1.0 mmol), **2** (2.5 mmol), 10 mol % $Cu(BF_4)_2$/AC in 2.0 mL of MeOH. The reaction was performed using DTBP (2.0 mmol), open flask. [b]Isolated yields.

82% (entry 6). With more steric hindrance existing, the yields significantly decreased (**3d**, **3e** vs **3b**). *Di*-methyl at the *m*-position performed better than at the *o*-position (**3e** vs **3d**). Some sorts of *m*-substituted aromatic boronic acids undergo reaction smoothly, such as methyl, nitro, and methyl formate (MF) groups (**3f**, **3l**, **3m**). Entirely different yields from the same substituted group but in a different position indicated that the electron-withdrawing effect by *o*-F or Br significantly affected the efficiency of C−N bond formation (**3h** vs **3j**, **3i** vs **3k**).

Next, we turned our attention to exploring the scope of various substituted anilines (entries 14−21). For *para*-substituted anilines, both electron-donating (*tert*-butyl, methyl) and electron-withdrawing groups (NO_2, Br, and Cl) can be equally applied with acceptable yields (**3n**, **3o**, **3p**, **3g**, **3k**). And the yield of **3q** was decreased to 59% in the presence of a strong electron-withdrawing group, trifluoromethyl. In contrast, two halogen atom-substituted product **3r** was obtained in a relatively lower yield (68%, **3r** vs **3o** and **3k**). And *N*-arylation of 4-(piperidin-1-yl)aniline proceeded well (**3s**, entry 23). Interestingly, for the synthesis of 2-F-*N*-phenylaniline, two different yields in two ways indicated that the effect of *ortho*-F might be more powerful in transmetallation than that of the reductive elimination process (**3h**, entry 8 vs 21).

The scope of $Cu(BF_4)_2$/AC-catalyzed C−N bond formation was further extended to the coupling reaction of substituted aryl boronic acids with isoquinolin-1(2*H*)-one and 1,6-naphthyridin-5(6*H*)-one (Table 4). TMEDA was a good organic base choice for Chan−Lam amination (**3a**, Table 1). And we were gratified to find that using TMEDA and a mixed solvent of THF and methanol for both electron-withdrawing and electron-donating substituents on aryl boronic acids were well tolerated to give corresponding products with good to excellent yields.

For 1,6-naphthyridin-5(6*H*)-one, not many differences in **6a**-**6d** and **6m** indicated a little impact of steric hindrance exerted by an electron-rich *ortho*-alkyl substituent. Similarly, coupling of isoquinolin-1(2*H*)-one with *ortho*-substituted aryl boronic acids also afforded the products in about 99% yields (**6n**-**6p**). Both electron-donating and electron-withdrawing groups at the *meta*-position, including double methyl-substituted (**6e**, **6t**), methyl (**6f**), Br (**6g**, **6v**), NO_2 (**6h**, **6r**), and methoxycarbonyl (**6i**, **6s**), worked well across the two different substrates. The strong electron-withdrawing effect of *ortho*-Br reduced the efficiency (**6j**, **6u**). In addition, *ortho*-hydroxy (**6k**, **6q**) substituted aryl boronic acids were also well reactive. Interestingly, hydrolysis completely proceeded to the amide group in situ when using *ortho*-CN-phenylboronic acid (**6l**). This result indicated that our heterogeneous catalyst can be used for cyanide hydrolysis.

N-Arylation of naphthyridinone proceeded with a better yield than that of isoquinolinone with the same substituents. The proposed reason might be that the elimination of nitrogen atoms from naphthyridinone reduces the nucleophilicity of amide-NH. Otherwise, the phenylation of pyridazine-3(2*H*)-one and quinolin-2(1*H*)-one was significantly reduced, which could be due to the π-deficient effect (**6w**, **6x**).

Next, control experiments were carried out to understand the plausible reaction mechanism (Scheme 3). Only azobenzene formation was observed within the aq. $Cu(BF_4)_2$-catalyzed reaction (Scheme 3i and Table S1, entry 5). After using the molecule sieves, biphenyl became the main byproduct, and the ratio to azobenzene was close to 4:1 (Scheme 3ii and Table S4). A small number of byproducts containing phenol, anisole, and diphenyl ether also existed (Table S4) in the $Cu(BF_4)_2$/AC-catalyzed reaction (Scheme 3iii). The results showed biphenyl, phenol, and diphenyl ether perhaps derived from phenylboronic acid. We extended the rotary evaporation time in the preparation of $Cu(BF_4)_2$/AC to eliminate the effect of H_2O. The formation of biphenyl was still observed under open-flask conditions (TLC detection, Table 1, entry 14, and Scheme 3iv). Further performing the reaction with DTBP, the homocoupling of phenylboronic acid did not occur (not detected in TLC, Scheme 3v). The reaction could also be carried out under a N_2 atmosphere. However, there were more byproducts in a frightful mess (Scheme 3vi, TLC detection). Finally, in the absence of air and DTBP, the formation of diphenylamine and biphenyl was not observed (Scheme 3vii), proving that an oxidant is essential for the Chan−Lam coupling and homocoupling of phenylboronic acid.

The currently accepted catalytic cycle for Chan−Lam coupling is the one proposed by Stahl, in which the arylated Cu(II) complex is oxidized to arylated Cu(III) by another Cu(II) prior to reductive elimination.[17,34−36] And based on the experimental results and previous literature about the possible mechanism for phenylboronic acid homocoupling,[37] a tentative mechanism is shown in Scheme 4. The first step is the reaction of $Cu(BF_4)_2$/AC and aryl boronic acids, resulting in the formation of complex **A**. Next, oxidation of **A** to the Cu(III) complex **B** occurs by the disproportionation reaction, which liberates a Cu(I) intermediate. Reductive elimination of arylamines affords

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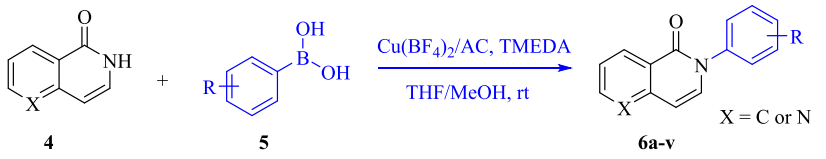
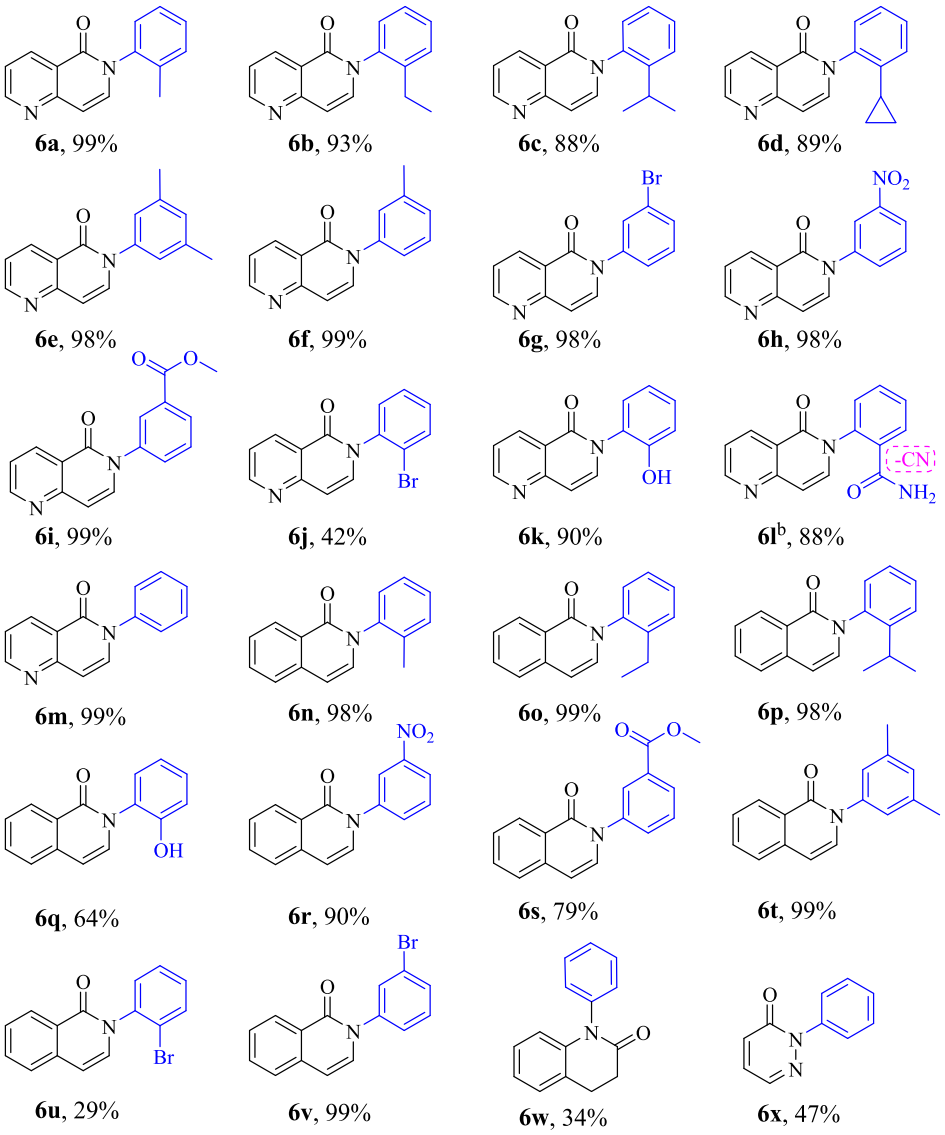
Table 4. $Cu(BF_4)_2$/AC-Catalyzed the Coupling of 1,6-Naphthyridin-5(6*H*)-one or Isoquinolin-1(2*H*)-one with Substituted Phenylboronic Acids[a,b]



4 5 6a-v



[a]All reactions were performed with **5** (2.5 equiv to 1.0 mmol of **4**), 10 mol % $Cu(BF_4)_2$/AC, TMEDA (3.0 equiv), THF (4.0 mL), and MeOH (6.0 mL). [b]Only amide compound. All yields were isolated.

N-arylated products and gives the Cu(I) intermediate. The oxidative dimerization mechanism of aryl boronic acids involved the Cu(I) species. And compared to O_2, DTBP might facilitate the reoxidation of the Cu(I) intermediate to the Cu(II) catalyst. It is not clear but possibly be the reason for less biphenyl formation.

The recyclability of the prepared catalyst was tested using aniline and phenylboronic acid as substrates (Table 3, entry 1). The catalyst was easily separated from the reaction mixture by filtration. The recovered catalyst was washed with ethyl acetate and dichloromethane, then dried and reused for the same reaction. No significant decrease in catalyst activity was observed for up to 5 runs (Figure 1). Furthermore, when the conversion was 60% (4 h), we separated $Cu(BF_4)_2$/AC from the reaction mixture and washed it with methanol. The filtrate was stirred for an additional 6 h. No further reactivity was observed in the reaction solution. These results indicated the heterogeneous characteristics of $Cu(BF_4)_2$/AC.

Finally, the catalyst was further profiled by the Brunauer–Emmett–Teller (BET) method, X-ray diffractometer (XRD), scanning electron microscope (SEM), and X-ray photoelectron spectroscopy (XPS).[38,39] Our catalyst has a Brunauer–Emmett–Teller (BET) specific surface area of 675.0 $m^2\ g^{-1}$. And the pore volume was 0.42 $m^3\ g^{-1}$ (Figure 2a). Due to the

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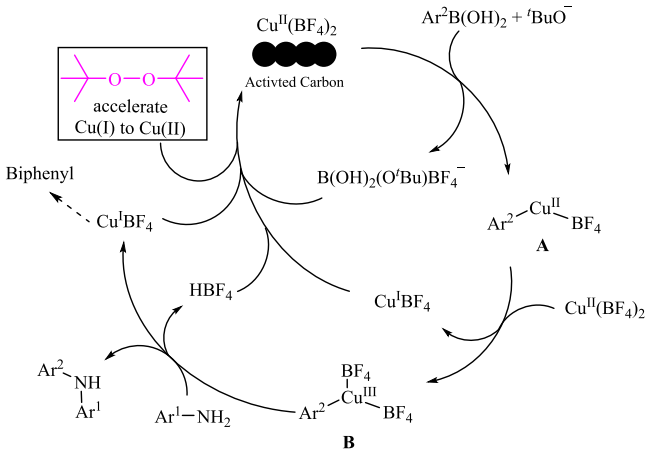
Scheme 4. Proposed Mechanism



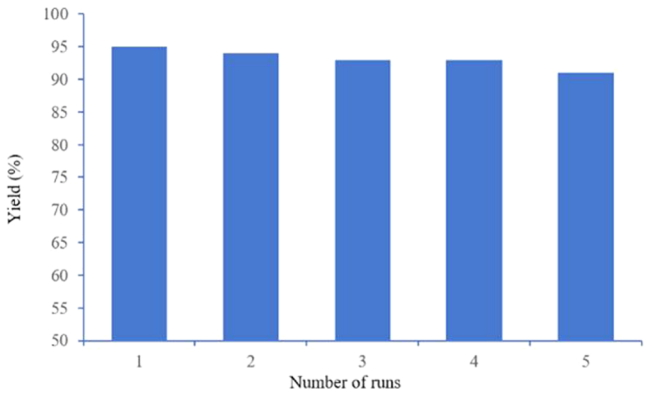


Figure 1. Recyclability of the catalyst.

low content of copper salt, the graph showed the amorphous nature of the material as a major portion of the material constitutes activated carbon (Figure 2b). However, the scanning electron microscopy (SEM) images and the wide-scan XPS spectrum of $Cu(BF_4)_2$/AC shown in Figure 2c,d revealed that copper salt was coated on activated carbon successfully. And the chemical state of copper mainly existed as Cu^{2+} valence and was assigned to Cu $2p_{3/2}$ at a binding energy of 932.1 eV.

CONCLUSIONS

In summary, an efficient activated carbon-supported $Cu(BF_4)_2$-catalyzed Chan−Lam coupling method has been developed. During the synthesis of substituted diphenylamine, the amination method with phenylboronic acids involving base-free and DTBP as the oxidant showed broad substrate scope and produced the corresponding coupling products in moderate to excellent yields with low catalytic loadings at room temperature. This methodology could also be successfully applied for the synthesis of novel 2-phenylisoquinolin-1(2*H*)-one and 6-phenyl-1,6-naphthyridin-5(6*H*)-one derivatives. Further detailed study of the mechanism of this reaction is ongoing, and results will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04299.

Experimental procedures, NMR spectra data, and MS of all new compounds (PDF)

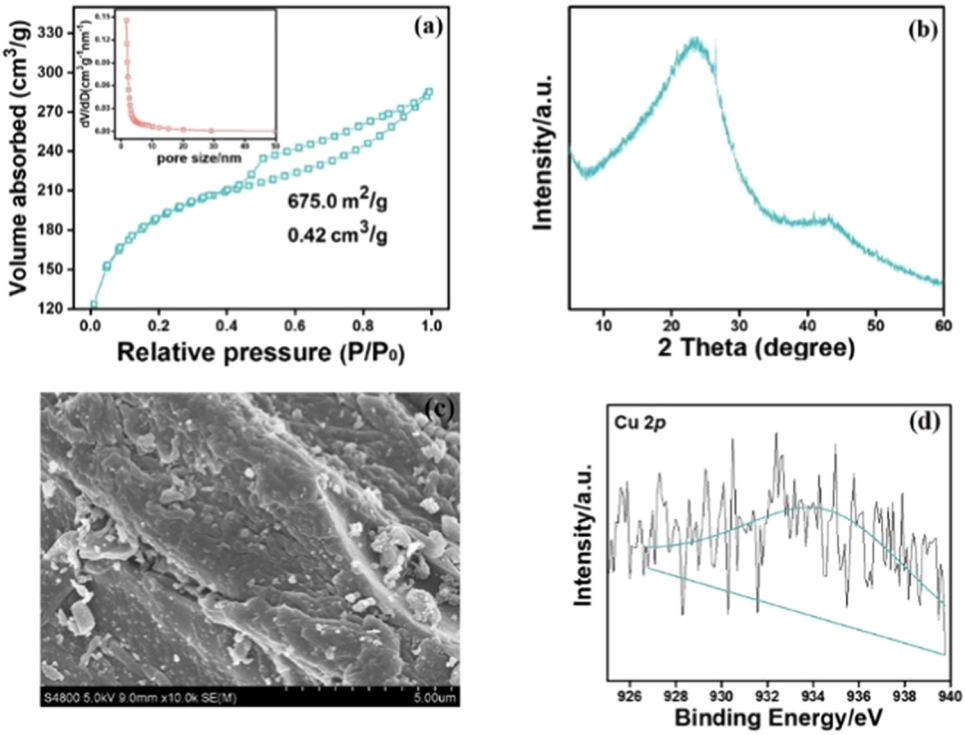


Figure 2. Characterization of the $Cu(BF_4)_2$/AC (a) specific surface area and pore size determined by the BET method. (b) XRD of $Cu(BF_4)_2$/AC. (c) SEM image. (d) XPS of $Cu(BF_4)_2$/AC.

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Notes

The authors declare no competing financial interest.

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