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Copper-Catalyzed C–NH_2 Arylation of 2-Aminobenzimidazoles and Related C-Amino-NH-azoles

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Abstract: A copper(II)-catalyzed selective C–NH_2 arylation of 2-aminobenzimidazoles and related C-amino-NH-azoles was achieved in presence of 2,2′-bipyridine and cesium carbonate at 60 °C under open air conditions and this is first method for the copper-catalyzed selective C–NH_2 arylation in the presence of other reactive nucleophilic sites. Previously unexplored heteroaromatics possessing multiple nucleophilic sites that are selectively arylated at the C–NH_2 position are obtained, providing an exceptional tool for rapid delivery of a diverse array of medicinally important C–NH(aryl) derivatives of aminoazoles without any protection/deprotection of ring N–H bonds. It is first example for the selective C–NH_2 arylation of 5-aminoindazole, 4-aminopyrazole, 5-aminopyrazole, 9*H*-purine-6-amine, and 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine derivatives.

Keywords: aminoazoles; Chan–Lam coupling; copper catalysts; open-flask chemistry; selective N-arylation

Introduction

Transition metal-catalyzed N-(hetero)arylation reactions have emerged as powerful synthetic tools in organic synthesis.[1] Designing and/or optimizing catalytic systems for substrates with multiple heteroatom sites capable of undergoing cross-coupling reactions is a real challenge to the organic chemist. In particular, selective N-arylation of heteroaromatics possessing multiple nucleophilic sites without protection/deprotection, while challenging, would be valuable as it rapidly generates molecular complexity in designed molecules with minimal synthetic manipulations. In this context, spectacular advancements have been made in the efficient construction of selective C–N bonds for many biologically potential substrates containing multiple nucleophilic sites (e.g., purines, aminobenzamides, aminoindoles, pyridinones, aminophenols, guanidines, unsymmetrical imidazoles, triazoles, etc.) capable of undergoing reaction. However, most of these kinds of chemo/regioselective C–N bond formation protocols are realized by metal-catalyzed coupling reactions, which mainly includes Buchwald–Hartwig and Ullmann-type reactions promoted by palladium, and/or copper, as catalyst.[2]

N-Arylated 2-aminobenzimidazoles, particularly the C-2–NH_2 arylated 2-aminobenzimidazoles, are a privileged heterocyclic class found in a variety of medicinally important compounds such as Tie-2 kinase inhibitors,[3] aurora kinase inhibitors,[4] and integrin $\alpha_4\beta_1$ antagonists[5] (Figure 1). Thus, the selective N-arylation of these amino-N-heterocycles without protecting one nucleophilic site (e.g., 2-aminobenzimidazole, 3-aminopyrazole, 3-aminoindazole, 5-aminoindazole, 9*H*-purine-6-amine, 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine) is synthetically important as it provides direct access to a diverse array of potentially bioactive N-arylated derivatives. Because of the potential challenges in the case of 2-aminobenzimidazole they represent a unique structural class where such an approach includes the formation of regioisomers and/or polyarylated products due to the presence of three adjacent nucleophilic nitrogens (N-1, N-3 and C-2 amino group). The tautomeric nature of 2-aminobenzimidazoles makes them a very attractive target for selective N-arylation (Scheme 1).

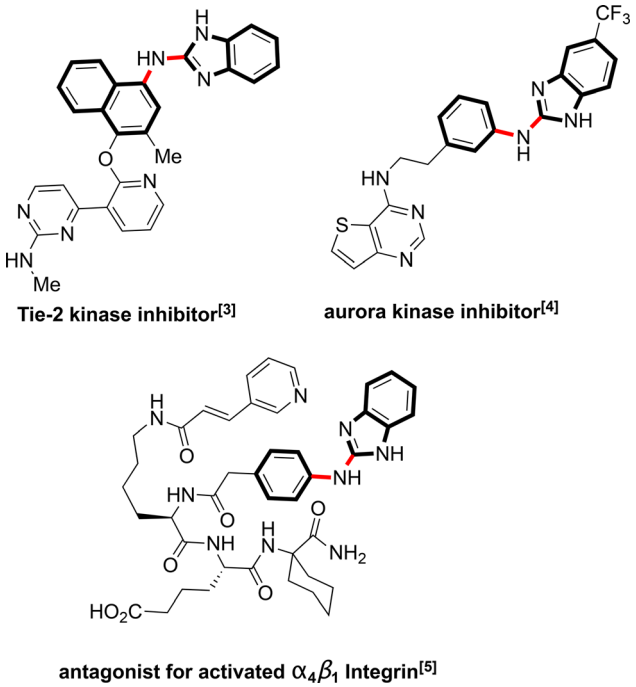
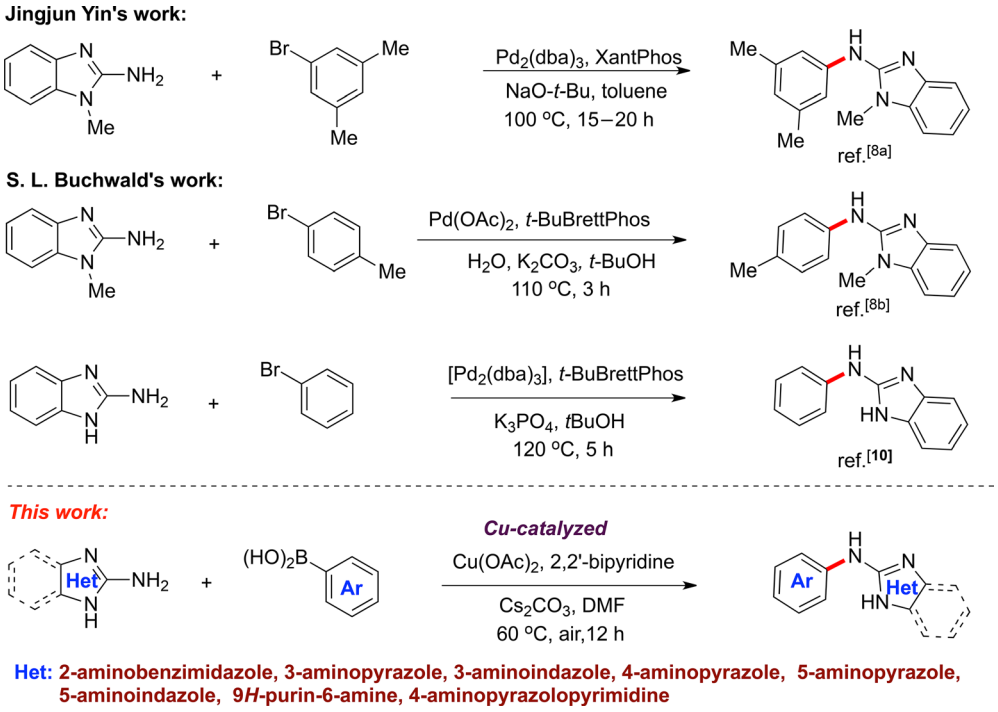


Figure 1. Biologically active compounds containing C-2 NH-arylbenzimidazole subunits.

Many efficient Cu-and Pd-catalyzed N-1 arylations of NH-azole derivatives have been reported.[6,7] In this context, arylation of the C-2 NH_2 group has been carried out initially with N-1 protected 2-aminobenzimidazoles.[8] Previously it was observed that arylation happened selectively at the N-1 position of unprotected 2-aminobenzimidazoles by using different N,N-bidentate and O,O-bidentate ligands under modified Ullmann-type coupling conditions.[9] In 2012 Buchwald et al. developed elegant Pd-catalyzed conditions for the chemoselective C-2 NH_2 arylation of 2-aminobenzimidazoles for the first time.[10] Copper-catalyzed arylboronic acid-promoted N/O-arylation, now referred as Chan–Lam-type coupling, has emerged as a powerful synthetic tool.[11] The reasons behind the popularity of this reaction are the mild reaction conditions and the ability to use an ambient atmosphere ('open-flask chemistry').[12] In due course, some examples of modified Chan–Lam-type of coupling conditions have been developed for the selective N-arylations of aryl/heteroaromatic compounds containing multiple nucleophilic sites.[13] But to the best of our knowledge, copper-catalyzed methods for selective C–NH_2 arylation of C-amino-NH-azoles have never been described. During our work on the copper-catalyzed, boronic acid-promoted, N-arylation of nitrogen-containing heterocycles,[14] recently we have developed a method for the N-1 arylation of C-amino-NH-azoles.[14b] We became interested in using 2-aminobenzimidazoles as potential substrates for selective C-2 NH_2 arylation (Scheme 1). Herein, we report the Cu-catalyzed conditions for the selective C–NH_2 arylation of unprotected 2-aminobenzimidazoles and other related C-amino-NH-azoles.



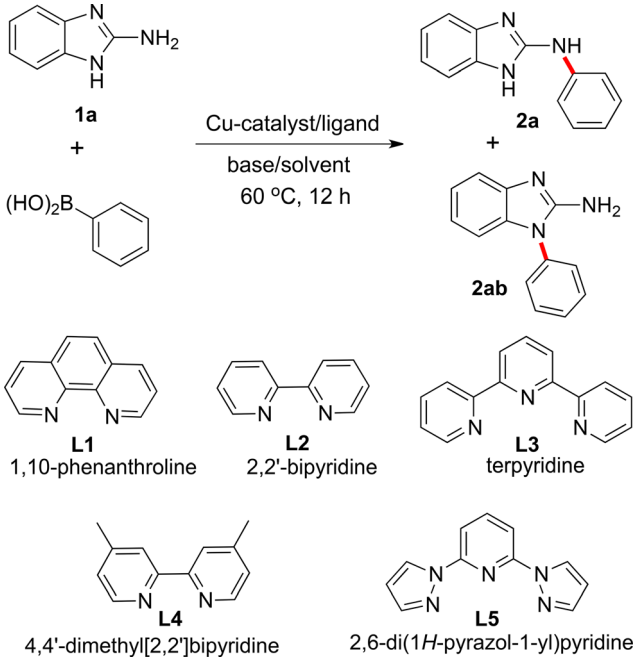
Scheme 1. Approaches for the C–NH_2 arylation of C-amino-NH-azoles.

Results and Discussion

During our previous studies[14b] we have observed that the selective arylation occurred in the ring N-1 H, which may be due to the higher acidity of the ring N–H when compared with the C–NH_2 bond of C-amino-NH-azoles. Thus, the use of ligand and/or base combination may be necessary for changing the selectivity pattern (N-1 *vs.* C–NH_2). To facilitate the reaction for C–NH_2 arylation of C-amino-NH-azoles according to our observations, we thought that the addition of nitrogen-containing ligands would be a good starting point.[2e] Initially we started our screening of the reaction conditions with 2-aminobenzimidazole (**1a**) by using a $Cu(OAc)_2$/CsOPiv combination in DMF at 60 °C, and we isolated the major N-1 arylated product (**2ab**, 80%) along with a trace amount of C-2 NH_2 arylated product (**2a**) (Table 1, entry 1). When we tried to change to different bases (K_2CO_3, Cs_2CO_3) the product yield was not improved (Table 1, entries 2 and 3). Then we added 1,10-phenanthroline (**L1**) as a ligand in the presence of Cs_2CO_3 in DMF at 60 °C. The required C-2 NH_2-arylated product (**2a**) was isolated in 80% yield, with no formation of the N-1 arylated product (Table 1, entry 4). Bases such as K_3PO_4, Na_2CO_3 and NaOAc remain inferior to the $Cu(OAc)_2$/1,10-Phen combination, as the products were formed in the range of 30–40% (Table 1, entries 5–7). When $Cu(OTf)_2$ was used as the Cu source, the product was isolated in 65% yield (Table 1, entry 8). Next we used 2,2′-bipyridine (**L2**) as a ligand instead of 1,10-phenanthroline (**L1**), and the desired C-2 NH_2 arylated product (**2a**) was obtained in 85% yield (Table 1, entry 9). The other nitrogen ligands such as terpyridine (**L3**), 4,4′-dimethyl[2,2′]bipyridine (**L4**) and 2,6-di(1*H*-pyrazol-1-yl)pyridine (**L5**) were less effective (Table 1, entries 10–12) in this cross-coupling reaction. We observed that the combinations of **L2** as a ligand with other bases such as K_3PO_4, Na_2CO_3, NaOAc, *t*-BuOK and KOH were less effective (Table 1, entries 13–17). Screening of different solvents did not help in improving the yield (Table 1, entries 18 and 19). A relatively lower yield was obtained when we employed $Cu(OTf)_2$ as a catalyst (Table 1, entry 20). We have also attempted different reaction temperatures, but 60 °C was found to be optimal for smooth coupling. When we increased the reaction temperature **2a** was isolated in lower yield, and at room temperature no product formation was observed (for details see the Supporting Information). Furthermore by varying the catalyst/ligand ratio it was observed that $Cu(OAc)_2$ (0.2 equiv.) and **L2** (0.2 equiv.) afforded the highest yield of the product **2a** (for detailed optimization of reaction conditions, see the Supporting Information).

Under the optimized reaction conditions, first we examined the scope of various boronic acids with 2-aminobenzimidazole (Table 2). The reaction went smoothly with different arylboronic acids to give the desired C-2 NH_2 arylated products (**2a–y**) in excellent yields (65–90%). Arylboronic acids with *para*-substituted groups such as 4-Me (**2b**), 4-propyl (**2c**), 4-cyclopentyl (**2d**), 4-OMe (**2e**), 4-OEt (**2f**), 4-Br (**2h**), 4-F

Table 1. Optimization of the reaction conditions[a]

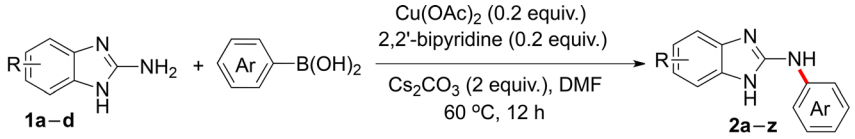


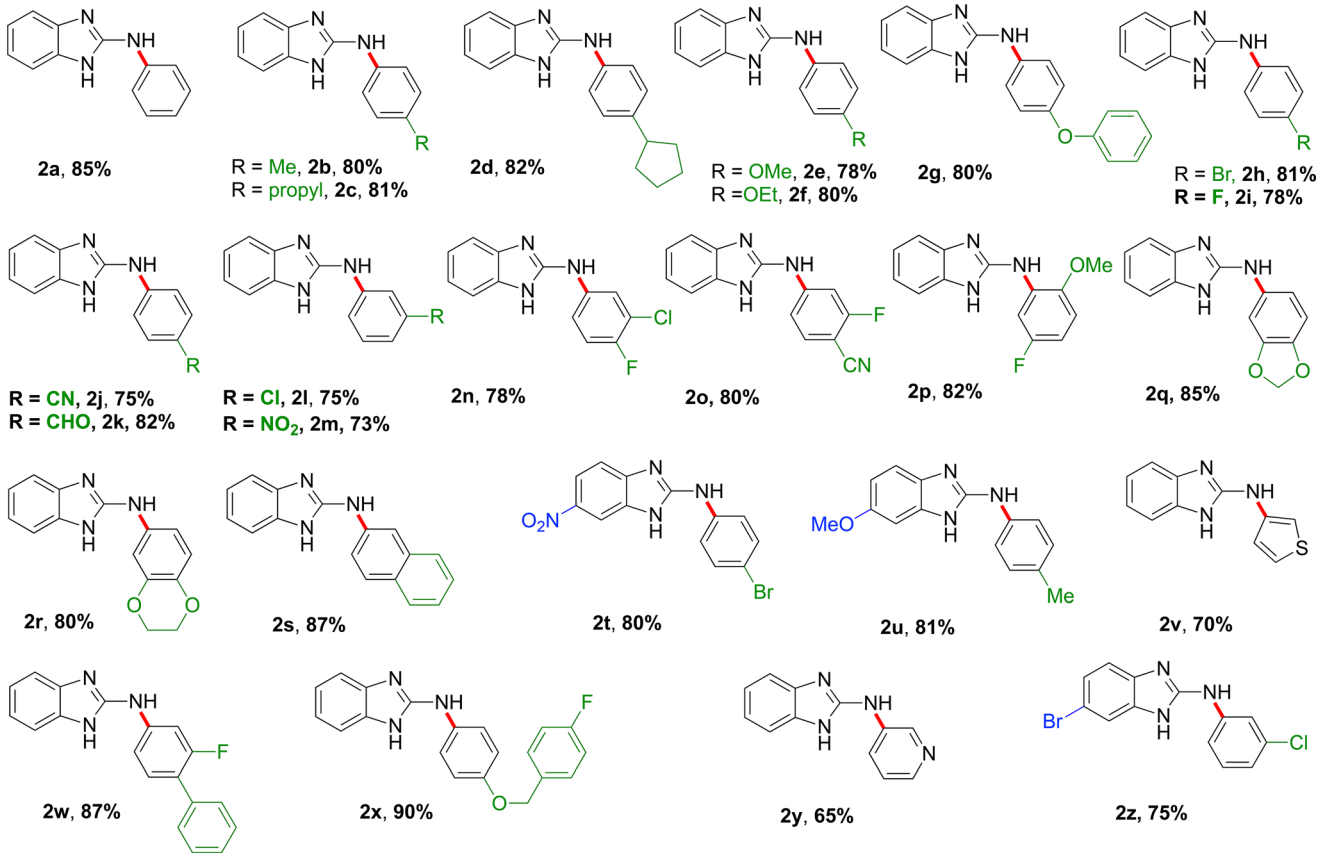
Entry	Catalyst	Ligand	Base	Solvent	Yield [%][b] of **2a/2ab**
1	$Cu(OAc)_2$	–	CsOPiv	DMF	trace/80
2	$Cu(OAc)_2$	–	K_2CO_3	DMF	trace/60
3	$Cu(OAc)_2$	–	Cs_2CO_3	DMF	trace/40
4	$Cu(OAc)_2$	**L1**	Cs_2CO_3	DMF	80/00
5	$Cu(OAc)_2$	**L1**	K_3PO_4	DMF	35/00
6	$Cu(OAc)_2$	**L1**	Na_2CO_3	DMF	40/00
7	$Cu(OAc)_2$	**L1**	NaOAc	DMF	30/00
8	$Cu(OTf)_2$	**L1**	Cs_2CO_3	DMF	65/00
9	**$Cu(OAc)_2$**	**L2**	**Cs_2CO_3**	**DMF**	**85/00**
10	$Cu(OAc)_2$	**L3**	Cs_2CO_3	DMF	60/00
11	$Cu(OAc)_2$	**L4**	Cs_2CO_3	DMF	82/00
12	$Cu(OAc)_2$	**L5**	Cs_2CO_3	DMF	70/00
13	$Cu(OAc)_2$	**L2**	K_3PO_4	DMF	40/00
14	$Cu(OAc)_2$	**L2**	Na_2CO_3	DMF	50/00
15	$Cu(OAc)_2$	**L2**	NaOAc	DMF	60/00
16	$Cu(OAc)_2$	**L2**	*t*-BuOK	DMF	20/00
17	$Cu(OAc)_2$	**L2**	KOH	DMF	55/00
18	$Cu(OAc)_2$	**L2**	Cs_2CO_3	DMSO	70/00
19	$Cu(OAc)_2$	**L2**	Cs_2CO_3	DMA	55/00
20	$Cu(OTf)_2$	**L2**	Cs_2CO_3	DMF	75/00

[a] *Reaction conditions:* 2-aminobenzimidazole (1.0 equiv.), phenylboronic acid (1.2 equiv.), $Cu(OAc)_2$ (0.2 equiv.), 2,2′-bipyridine (0.2 equiv.), Cs_2CO_3 (2.0 equiv.) DMF (1 mL), 60 °C, 12 h, air.

[b] Isolated yield.

Table 2. Scope of the Cu-catalyzed C2-NH_2-arylation of 2-aminobenzimidazoles.[a]



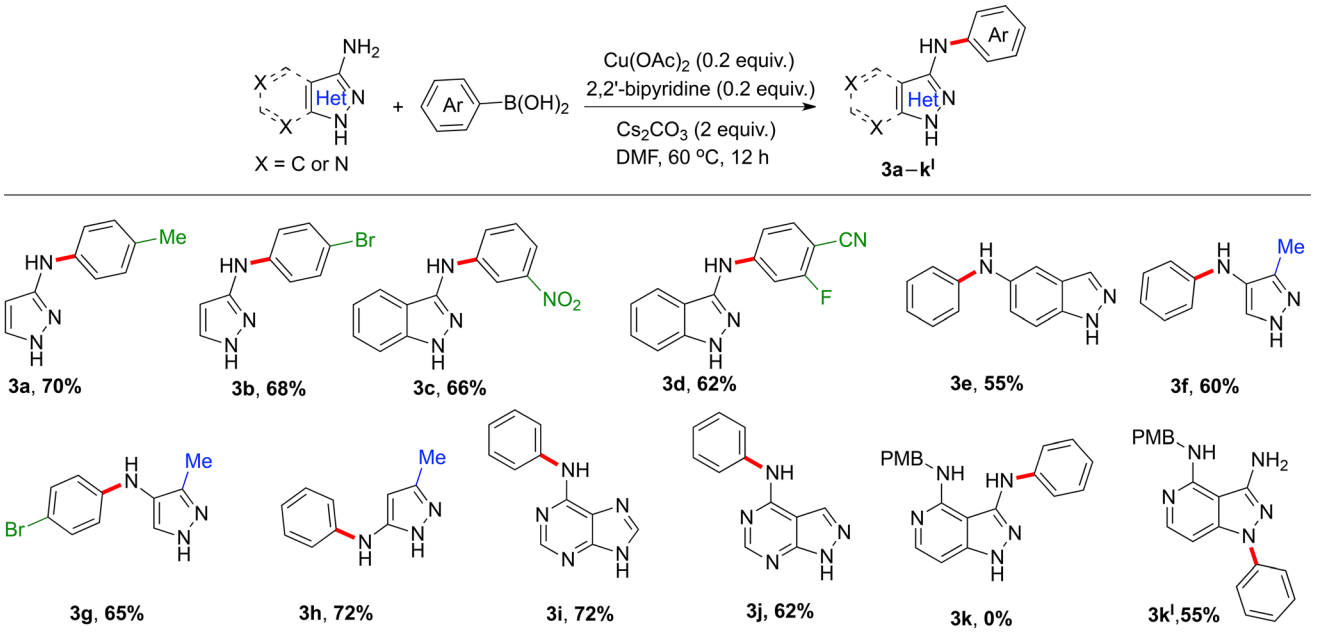


[a] *Reaction conditions:* 2-aminobezimidazole (1.0 equiv.), aryl/heteroarylboronic acid (1.2 equiv.), $Cu(OAc)_2$ (0.2 equiv.), 2,2′-bipyridyl (0.2 equiv.), Cs_2CO_3 (2.0 equiv.), DMF (1 mL), 60 °C, air, 12 h.

(**2i**) and *meta*-substituted groups 3-Cl (**2l**, 75%), 3-NO_2 (**2m**, 73%) afforded good yields and no other isomers were obtained. We observed that the electronic nature of the boronic acids did not have any influence in the reaction as both electron-rich (**2b–f**) and electron-poor (**2h–n**, **2p**) arylboronic acids resulted in excellent yields (73–82%). Functional groups such as 4-Br (**2h**, 81%), 4-CN (**2j**, 75%), 4-CHO (**2k**, 82%) are tolerated under the optimized conditions. The reaction was also performed with disubstituted phenylboronic acids, e.g., **2n** (3-Cl, 4-F), **2o** (3-F, 4-CN), **2p** (2-OMe, 5-F), and the N-arylated products were isolated in excellent yields (78–82%).

We have investigated three bicyclic boronic acids. In the case of 2-naphthylboronic acid the yield is 87% (**2s**) whereas benzo[*d*][1,3]dioxol-5-ylboronic acid resulted in **2q** in 85% yield and (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl) boronic acid afforded **2r** in 80% yield. To enhance the substrate scope, the reaction was tested with substituted 2-aminobenzimidazoles. When we tested 6-nitro-2-aminobenzimidazole with 4-bromophenylboronic acid the yield is 80% (**2t**), while on using 6-methoxy-2-aminobenzimidazole with 4-methylphenylboronic acid we obtained the N-arylated product in 81% yield (**2u**) and by using 6-bromo-2-aminobenzimidazole with 3-chlorophenylboronic acid the yield is 75% (**2z**). The further scope of this reaction was tested with different heterocyclic boronic acids, e.g., 3-thienyl- (**2v**) and 3-pyridylboronic acid (**2y**) and the C-2 NH_2 arylated products were obtained in good yield (**2v**, 70%; **2y**, 65%). A further evaluation of the scope of this method revealed that the reaction also proceeded smoothly with (2-fluoro-[1,1′-biphenyl]-4-yl)boronic acid (**2w**, 87%), and [4-(4-fluorobenzyloxy)phenyl]boronic acid (**2x**, 90%), gave excellent yields under these optimized reaction conditions (Table 2).

Table 3. Selective C–NH_2 arylation of C-animo-NH-azoles.[a]



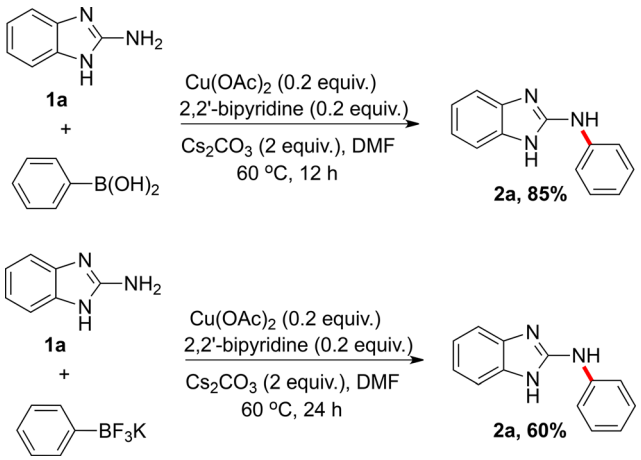
[a] *Reaction conditions:* C-amino-NH-azole (1.0 equiv.), arylboronic acid (1.2 equiv.), $Cu(OAc)_2$ (0.2 equiv.), 2,2′-bipyridyl (0.2 equiv.), Cs_2CO_3 (2.0 equiv.), DMF (1 mL), 60 °C, air, 12 h.

Encouraged by the versatility of this cross-coupling reaction, we decided to enhance the substrate scope. The aminoindazoles/pyrazoles are privileged heterocyclics as they are found in many biologically active compounds.[15] When we carried out this reaction with 3-aminopyrazole (Table 3) under the optimized reaction conditions, various boronic acids coupled to give exclusively the C-3 NH_2 arylated products (4-Me: **3a**, 70%; 4-Br: **3b**, 68%). Reaction of 3-aminoindazole with 3-nitrophenylboronic acid gave exclusively the C-3 NH_2 arylated product (**3c**, 66%) while disubstituted phenylboronic acid resulted (**3d**) in 62% yield. 5-Aminoindazole reacted smoothly with phenylboronic acid in giving exclusively C–NH_2 arylated product (**3e**) in moderate yield (55%). By using 4-aminopyrazole and 5-aminopyrazole with arylboronic acids, it was found that the reaction was occurred selectively at the C–NH_2 position (**3f**, 60%; 4-Br: **3g**, 65%; **3h**, 72%).

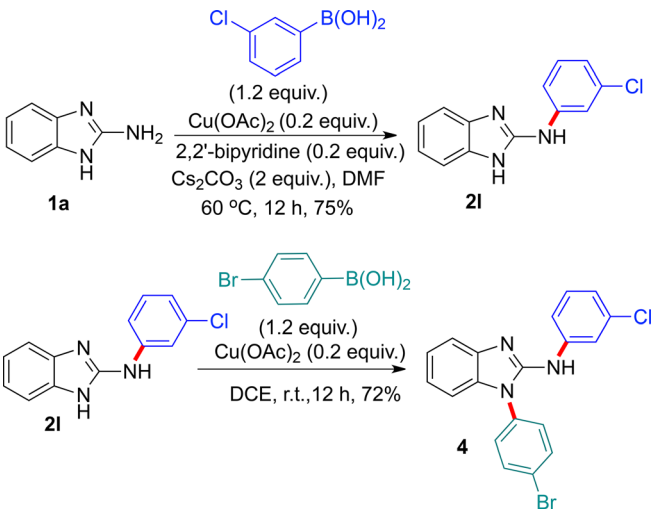
To enhance the substrate scope further, C–NH_2 arylation was performed with medicinally important heterocycles (e.g., 9*H*-purin-6-amine and 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine), under optimized conditions and the coupled N-arylated products were isolated in good yields (**3i**, 72%; **3j**, 62%). It is worthy to mention that previously no method was reported for the selective C–NH_2 arylation of these medicinally important heterocycles. When we used PMB-protected 1*H*-pyrazolo[4,3-*c*]pyridine-3,4-diamine with phenylboronic acid, it gave selectively N-1 arylated product in moderate yield (**3k**, 0%; **3k′**, 55%) due to clouding of PMB protected 4-amino group adjacent to the 3-animo group (Table 3).

Next, we did the reaction of 2-aminobenzimidazole with potassium phenyltrifluoroborate to extend this method to another aryl source under optimized reaction conditions, it was observed that reaction was inefficient as compared to the reaction with phenylboronic acid and the corresponding product was isolated in lower yields (**2a**, 60%) aftert a longer reaction period of 24 h (Scheme 2).

Then we became interested in the synthesis of diarylaminoazoles, for this reason **2l** was treated with 4-



Scheme 2. Selective C-2 NH_2 arylation of 2-aminobenzimidazole.



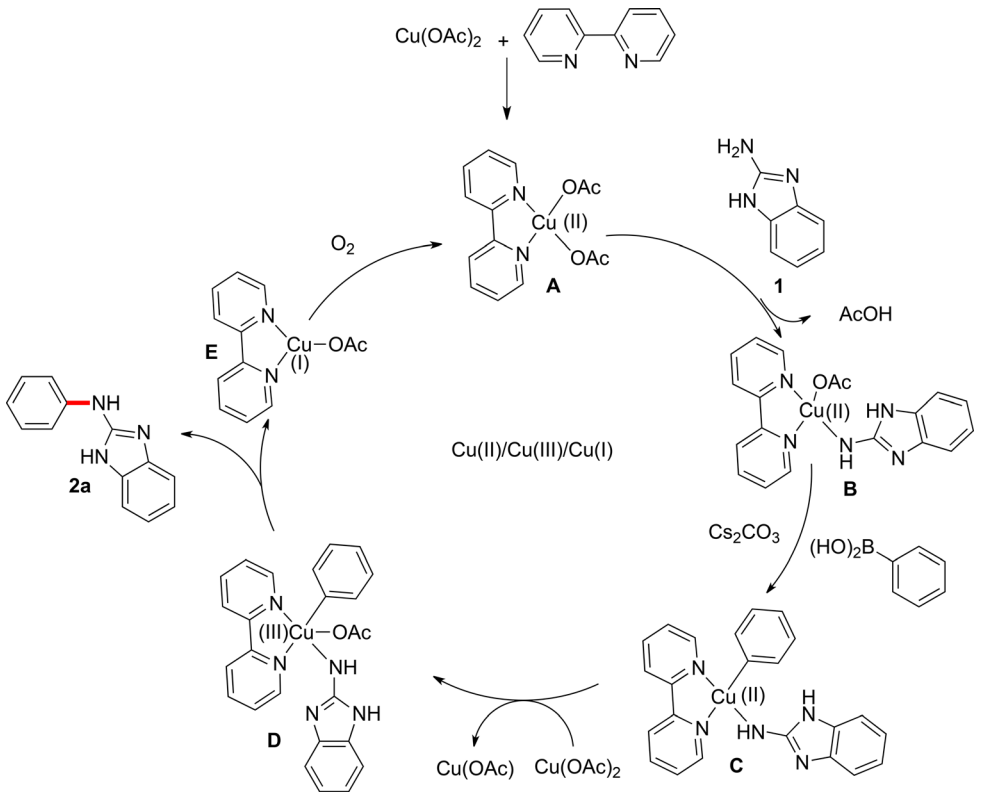
Scheme 3. Sequential two-step reaction for diarylamino-azoles.

bromophenylboronic acid catalyzed by $Cu(OAc)_2$ in dichloroethane to afford compound **4** (Scheme 3) in 72% yield (for screening of reaction conditions see the Supporting Information). Thus, this new two-step sequential protocol complements our previous method.[14b]

Although the reason for the selectivity at present is not clear, however, based on these results and previous literature reports,[16] we propose a plausible reaction mechanism (Scheme 4). The initial step involves the formation of Cu complex **A** generated from $Cu(OAc)_2$ and 2,2′-bipyridine (**L2)**, subsequently complex **A** and 2-aminobenzimidazole combine to form Cu(II) complex **B**. Phenylboronic acid then undergoes transmetallation with complex **B** to form Cu(II) complex **C** which, on disproportionation reaction, yields higher oxidation Cu(III) complex **D**.[16a,b] Now the Cu(III) complex **D** undergoes smooth reductive elimination to form the product **2a** with concurrent formation of Cu(I) complex **E**. Finally O_2 (air) acts as a terminal oxidant to regenerate Cu(II), thus completing the catalytic cycle.

Conclusions

In summary, we have developed a general, efficient, and ligand controlled copper(II)-catalyzed method for selective C–NH_2 arylation of 2-aminobenzimidazoles and related C-amino-NH-azoles. It was realized by using 2,2′-bipyridine as ligand and Cs_2CO_3 as base under open air conditions, and it is first method for the Cu-catalyzed selective C–NH_2 arylation in the presence of other reactive nucleophilic sites. The method is exemplified with various C-amino-NH-azoles and a broad selection of aryl/heteroarylboronic



Scheme 4. Plausible reaction mechanism.

acids. It is first example for the selective C–NH_2 arylation of 5-aminoindazole, 4-aminopyrazole, 5-aminopyrazole, 9*H*-purine-6-amine, and 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine derivatives. We believe that these new findings significantly broaden the scope of Chan–Lam-type coupling and definitely will add value in *de novo* design and development of Cu-catalyzed C–N bond formation reactions.

Experimental Section

General Information

All purchased chemicals were used without further purification. All reactions were performed under open air. Analytical thin layer chromatography was performed using TLC pre-coated silica gel 60 F254 Merck (20×20 cm). TLC plates were visualized by exposing UV light or by iodine vapors. Organic solutions were concentrated by rotatory evaporation on a Büchi (Switzerland) R-120 rotatory evaporator and vacuum pump V-710. Flash column chromatography was performed on Merck flash silica gel 100–200 mesh size. Melting points of solid compounds were determined on Büchi-B-545 (Switzerland) melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded with Bruker 500 and 400 MHz NMR instruments. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CHCl_3$ at 7.24 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm) or were recorded using tetramethylsilane (TMS) in the solvent of DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm;^{13}C NMR: DMSO at 40.0 ppm) or were recorded using tetramethylsilane (TMS) in the solvent of acetone-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, acetone at 2.09 ppm;^{13}C NMR: acetone at 29.9 ppm, 206.7 ppm). All the NMR spectra were processed in MestReNova. HR-mass spectra were recorded with an LCMS-QTOF Module No. G6540 A (UHD) instrument.

General Procedure A for the C–NH_2 Arylation of 2-Aminobenzimidazoles and Other C-Amino-NH-azoles

To a stirred solution of 2-aminobenzimidazole (1.0 equiv.) in DMF (1 mL) was added aryl/heteroarylboronic acid (1.2 equiv.) and $Cu(OAc)_2$ (0.2 equiv.), 2,2′-bipyridine (0.2 equiv.) and Cs_2CO_3 (2 equiv.) at room temperature. The reaction mixture was stirred at 60 °C for 12 h. The progress of the reaction was monitored by TLC and after completion of the reaction 10 mL of ice-cooled water were added to the reaction mixture at room temperature. The mixture was extracted with EtOAc (10 mL) further extracted two times with EtOAc (2×10 mL) and the combined organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography to give pure C-2 NH_2 arylated 2-aminobenzimidazoles (**2a–z**) and other C–NH(Ar) aminoazoles (**3a–k′**). Purified products were characterized by NMR, ESI-MS, and IR techniques.

General Procedure B for the Selective Two-Step Synthesis of Diarylated 2-aminobenzimidazoles (4)

To a stirred solution of *N*-(3-chlorophenyl)-1*H*-benzo[*d*]imidazol-2-amine (1.0 equiv.) in DCE (2 mL), 4-bromophenylboronic acid (1.2 equiv.) and $Cu(OAc)_2$ (0.2 equiv.) were added. The reaction mixture was stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC and, after completion of the reaction, 10 mL of water were added to the reaction mixture which was extracted then with EtOAc (10 mL), and further extracted two times with EtOAc (2×10 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified *via* flash chromatography (hexanes/EtOAc, 7:3) to provide the title compound **4** as an off-white solid. Purified product was characterized by NMR, ESI-MS, and IR techniques.

Acknowledgements

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