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Copper-catalyzed sequential *N*-arylation of *C*-amino-*NH*-azoles†

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Copper(II)-catalyzed boronic acid promoted C–N bond cross-coupling reactions have been successfully developed for sequential *N*-arylation of *C*-amino-*NH*-azoles. These general protocols are compatible with a variety of aryl/hetero-aryl boronic acids and provided rapid access to a diverse array of diarylaminoazole derivatives in a two-step sequence or in one-pot.

Transition-metal catalyzed N-(hetero) arylation is an important synthetic tool in organic chemistry.[1] Besides the traditional copper promoted Ullmann type coupling, the palladium-catalyzed reactions championed by Buchwald and Hartwig has been a major breakthrough in this area. However, the application of palladium- and copper-mediated *N*-arylation reactions in the synthesis of *N*-arylated heterocyclic compounds with medicinal properties not always straightforward often required optimized conditions particularly with the help of expensive ligands.[2] Furthermore, use of strong base and elevated temperature makes this procedure less attractive for functional group tolerability during structure activity relationship (SAR) and lead optimization study in medicinal chemistry.

Copper salt-promoting Chan–Lam type coupling reactions for the synthesis of *N*-aryl heterocyclic compounds have been extensively studied over the past few years.[3] The reason behind the popularity of this type of cross-coupling reaction is mild reaction conditions *e.g.* room temperature, weak base and ambient atmosphere (open-flask chemistry).[4] *N*-Aryl azoles are important building blocks in numerous agro chemicals, pharmaceuticals and biologically active compounds. Both Pd-and Cu-catalyzed efficient methods for N^1-arylation of azoles have been reported.[5,6] However, the transition metal-catalyzed *N*-arylation strategies have rarely been applied in selective *N*-arylation over other nucleophilic sites including aromatic amines of these important heterocycles

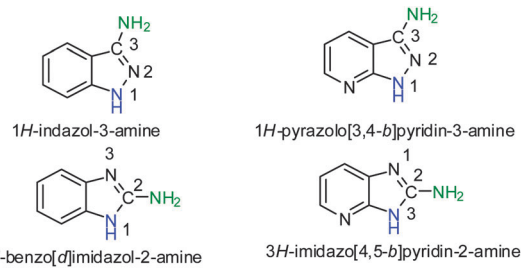
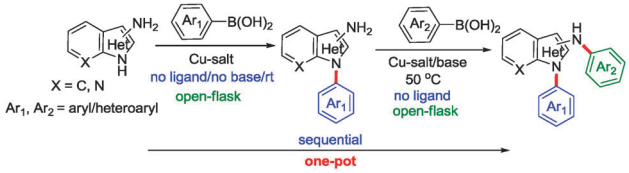


Fig. 1 Ary/hetroaryl-fused *C*-amino-*NH*-azoles.

(Fig. 1).[7] Therefore, the development of optimized catalytic conditions for the selective *N*-arylation of these heterocycles possessing multiple nucleophilic sites is much more challenging from the synthetic point of view. Furthermore, transition metal-catalyzed *N*-arylations using cyclic amidines (*e.g.* 2-aminobenzimidazole, 3-aminoindazoles, 3-aminopyrazolopyridine, 2-aminopyridoimidazoles) as substrates remain always challenging, as these functionalities coordinate strongly with reactive metals.[8] These limits need to be addressed with a strategy that can be widely applicable.

In particular we sought to explore reaction conditions for sequential *N*-arylation of *C*-amino-*NH*-azoles[9] (bearing different nucleophilic sites). We herein, report Cu-catalyzed boronic acid promoted *N*-arylation of *C*-amino-*NH*-azoles to access di-aryl amino azoles (Scheme 1) sequentially. To the best of our knowledge for the first time pyrazolopyridine and pyridoimidazole like substrates bearing two different nucleophilic sites have successfully been utilized in selective *N*-arylation.



Scheme 1 Selective *N*-arylation of *C*-amino-*NH*-azoles.

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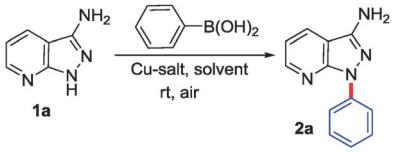
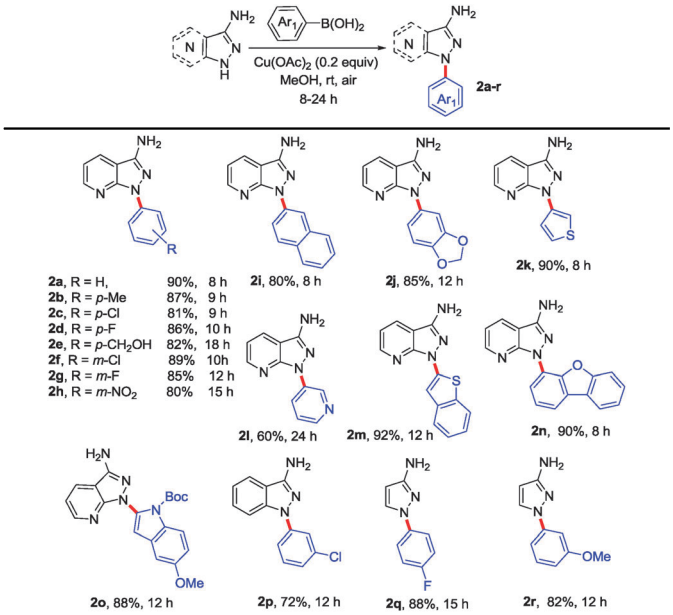
Table 1 Optimization studies on N^1-arylation of 1*H*-pyrazolo[3,4-*b*]pyridin-3-amine[a]



Entry	Catalyst	Solvent	Yield[b] (%)
1	$Cu(OAc)_2$ (1 equiv.)	DCE	n.r.
2	$Cu(OAc)_2$ (1 equiv.)	CH_3CN	45 (25)
3	$Cu(OAc)_2$ (1 equiv.)	MeOH	80
4	**$Cu(OAc)_2$ (0.2 equiv.)**	**MeOH**	**90**
5	$Cu(OAc)_2$ (0.2 equiv.)	DMF	10
6	$Cu(OAc)_2$ (0.2 equiv.)	DMSO	20
7	$Cu(OAc)_2$ (0.2 equiv.)	DME	n.r.
8	$Cu(OTf)_2$ (0.2 equiv.)	MeOH	50 (30)
9	CuI (0.2 equiv.)	MeOH	n.r.
10	Cu_2O (0.2 equiv.)	MeOH	n.r.
11[c]	$Cu(OAc)_2$ (0.2 equiv.)	MeOH	90
12[d]	$Cu(OAc)_2$ (0.2 equiv.)	MeOH	30
13[e]	$Cu(OAc)_2$ (1 equiv.)	DCM	20

[a] Reaction conditions: pyrazolopyridine (1.0 equiv.), phenylboronic acid (1.1 equiv.), $Cu(OAc)_2$ (0.2 equiv.), MeOH (2 mL), rt, air. [b] Isolated yield; the yield in parentheses refers to recovered starting material **1a**. [c] Reaction under 1 atm O_2. [d] Reaction under a N_2 atmosphere. [e] Et_3N (3 equiv.) used, n.r. = no reaction.

Table 2 N^1-Arylation of 1*H*-pyrazolo[3,4-*b*]pyridin-3-amine[a]



[a] Reaction conditions: 1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (1 equiv.), boronic acid (1.1 equiv.), $Cu(OAc)_2$ (0.2 equiv.), MeoH (2 mL), rt, air, 8–24 h.

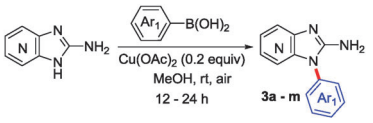
To find an effective catalytic system for the selective cross-coupling of *C*-amino-*NH*-azoles, our initial attempt was inspired by a method developed previously in our group for *N*-arylation of 2-amino-N-heterocycles.[10] The 7-aza derivative of 3-aminoindazole (*i.e.* 1*H*-pyrazolo[3,4-*b*]pyridine-3-amine,[11] **1a**) became an interesting choice as a model substrate due to its unique N-atom position in both the rings. Our initial attempt to perform the cross-coupling reaction of **1a** with phenylboronic acid (1.1 equiv.) by using $Cu(OAc)_2$ (1 equiv.) in DCE at room temperature (Table 1, entry 1) was not successful. To our delight by changing the solvent to CH_3CN the N^1-arylated product (**2a**) was isolated in 45% yield (Table 1, entry 2). When we used MeOH as the solvent (Table 1, entry 3), the yield improved dramatically (80%), perhaps due to the increased solubility of the reagents. Under these conditions the *N*-arylation is completely regioselective as only N^1-aryl azole was isolated.

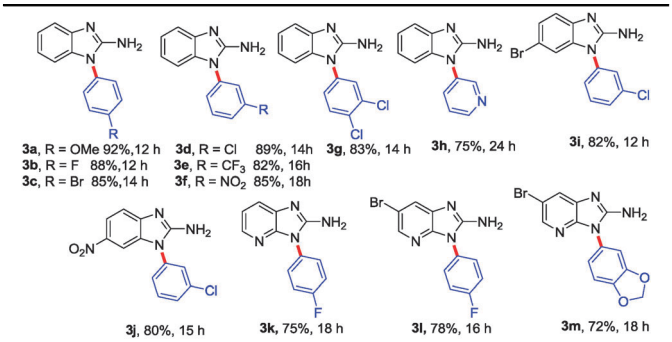
Encouraged by this promising result, we used a catalytic amount of $Cu(OAc)_2$ (0.2 equiv.) and the N^1-arylated product (**2a**) was isolated in 90% yield (Table 1, entry 4). Further screening showed that solvents like DMF (Table 1, entry 5) and DMSO (Table 1, entry 6) were not effective, while DME (Table 1, entry 7) failed to promote the reaction. We observed a sharp decline in yield when we replaced $Cu(OAc)_2$ with $Cu(OTf)_2$ (Table 1, entry 8). Other Cu-salts *e.g.* CuI (Table 1, entry 9) and Cu_2O (Table 1, entry 10) failed to give any cross-coupled product. Reaction under 1 atm O_2 did not show any further improvement in the yield of the reaction (Table 1 entry 11) while incomplete conversion and poor yields were observed under a N_2 atmosphere (Table 1 entry 12) suggesting that O_2 (air) plays a vital role in the catalytic cycle. Under standard Chan–Lam conditions (Table 1 entry 13) a mixture of products were formed and the isolated yield of the N^1-arylated product (**2a**) is only 20%.

Under the optimized reaction conditions, first we examined the scope of the boronic acids with 1*H*-pyrazolo[3,4-*b*]pyridine-3-amine[12] (Table 2). 1*H*-Pyrazolo[3,4-*b*] pyridine-3-amine underwent the reaction with different boronic acids to give the desired N^1-arylated products (**2a–h**) in excellent yields (80–90%). Boronic acids bearing both electron-donating (**2b**) and electron-withdrawing groups (**2c–h**) underwent the reaction smoothly and no other isomer or poly arylated product was formed. We have investigated two bicyclic boronic acids, in the case of 2-naphthylboronic acid the yield is 80% (**2i**) whereas benzo[*d*][1,3]dioxol-5-ylboronic acid resulted in 85% (**2j**) yield. The scope of this reaction was further tested with other heterocyclic boronic acids and to our expectation the N^1-arylated products (**2k–o**) were isolated in high yields. The only noticeable point, in the case of 3-pyridylboronic acid (**2l**) is the prolonged reaction time (24 h) with diminished yield (60%). A further evaluation of the scope of this methodology revealed that the reaction also proceeded smoothly with other *C*-amino-*NH*-azoles *e.g.* 3-aminoindazole and 3-aminopyrazole, providing access to N^1-aryl indazole (**2p**) and N^1-aryl pyrazoles (**2q–r**) in excellent yields (72–88%).

Next we focus our attention on selective N^1-arylation of another two important heterocycle 2-aminobenzimidazole[13] and 2-aminopyridoimdazole[14] (3*H*-imidazo[4,5-*b*]pyridin-2-amines). Synthetic challenges are associated with selective *N*-arylation of unprotected 2-aminobenzimidazole or 2-aminopyridoimdazole as the formation of regioisomer and/or poly arylated products due to the tautomeric nature of these heterocycles. To our delight under the optimized conditions various boronic acids coupled with 2-aminobenzimidazole to give N^1-selective arylated products (**3a–g**, Table 3). Under these optimized conditions N^2-arylated/poly-arylated (*C*-NH_2) products were not detected. Here also the electronic nature of the boronic acids did not play any significant role in the isolated yields (82–92%). In this context heteroaryl boronic acid was also examined,

Table 3 Cu-catalyzed N^1-arylation of 2-aminobenzimidazoles[a]



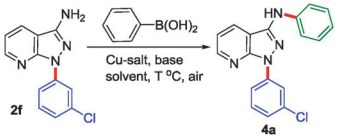


[a] Reaction conditions: 2-aminobenzimidazole (1 equiv.), boronic acid (1.1 equiv.), $Cu(OAc)_2$ (0.2 equiv.), MeOH (2 mL), rt, air, 12–24 h.

in the case of 3-pyridyl boronic acid the isolated yield is 75% (**3h**) in 24 h. To further enhance the substrate scope substituted 2-amino benzimidazoles were investigated, both 5-bromo and 5-nitro derivatives reacted with 3-chlorophenyl boronic acid to give N^1-arylated products in 82% (**3i**) and 80% (**3j**) yield respectively. Interestingly, both bromo and NO_2 functionalities were tolerated under these conditions, amenable to further functional group transformations. In recent days the imidazo[4,5-*b*]pyridine heterocycle, a versatile purine isostere and an important ring system was found to be useful in medicinal chemistry application of potential therapeutic benefits. Thus selective functionalization of this heterocycle will be interesting from the drug discovery point of view. To the best of our knowledge selective *N*-arylation of imidazopyridine is unexplored. With our optimized conditions we subjected 2-aminopyridoimdazole with different boronic acids and to our delight the *N*-arylation occurred selectively to give only the N^1-alkylated product (**3k–m**) in excellent yields (72–78%). Notably, no N^2-arylated/poly-arylated (*C*-NH_2) products were detected under these optimized conditions.

After successful optimization of regioselective N^1-arylation, we focused on exploring conditions for second *N*-arylation at the *C*-NH_2 position of *C*-amino-*NH*-azoles. Our initial attempt started with the reaction of 1-(3-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**2f**) and phenylboronic acid under Chan–Lam conditions and the reaction was unsuccessful (Table 4, entry 1). Then we used the inorganic base K_3PO_4 (1.5 equiv.) and DMF as the solvent at 100 °C with $Cu(OAc)_2$ (0.2 equiv.) as the catalyst. To our delight, the reaction afforded *N*-arylated heterocycle, **4a**, in 35% yield (Table 4, entry 2). It was found that employing CsOPiv[4a] (0.4 equiv.) as the base resulted in the best activity (87%, Table 4, entry 11) at 50 °C, while other bases such as Cs_2CO_3, K_2CO_3, Na_2CO_3, NaOAc, *t*BuOK and NaOPiv were less effective (Table 4, entries 3–8). We attempted different reaction temperatures, and 50 °C was found to be optimal (Table 4, entries 10 and 11). Screening of different solvents was also not effective in improving the further yield (Table 4, entries 12–14). A lower yield was obtained when employing $Cu(OTf)_2$ as a catalyst (Table 4, entry 15). Under the nitrogen atmosphere, only a small amount of **4a** was obtained (Table 4, entry 16).

Table 4 Optimization studies on C3-NH-arylation of 1-(3-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine[a]



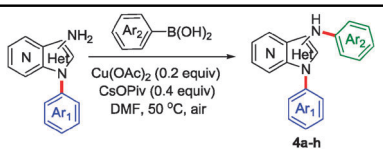
Entry	Catalyst	Base	Solvent	T (°C)	Yield[b] (%)
1[c]	$Cu(OAc)_2$	Et_3N	DCM	rt	n.r.
2	$Cu(OAc)_2$	K_3PO_4	DMF	100	35
3	$Cu(OAc)_2$	K_2CO_3	DMF	100	40
4	$Cu(OAc)_2$	CS_2CO_3	DMF	100	40
5	$Cu(OAc)_2$	Na_2CO_3	DMF	100	30
6	$Cu(OAc)_2$	NaOAc	DMF	100	55
7	$Cu(OAc)_2$	*t*BuOK	DMF	100	40
8	$Cu(OAc)_2$	NaOPiv	DMF	100	65
9	$Cu(OAc)_2$	CsOPiv	DMF	100	80
10[d]	$Cu(OAc)_2$	CsOPiv	DMF	100	82
11[d]	**$Cu(OAc)_2$**	**CsOPiv**	**DMF**	**50**	**87**
12	$Cu(OAc)_2$	CsOPiv	CH_3CN	50	50
13	$Cu(OAc)_2$	CsOPiv	MeOH	50	60
14	$Cu(OAc)_2$	CsOPiv	DMSO	50	40
15	$Cu(OTf)_2$	CsOPiv	DMF	50	45
16[e]	$Cu(OAc)_2$	CsOPiv	DMF	50	20

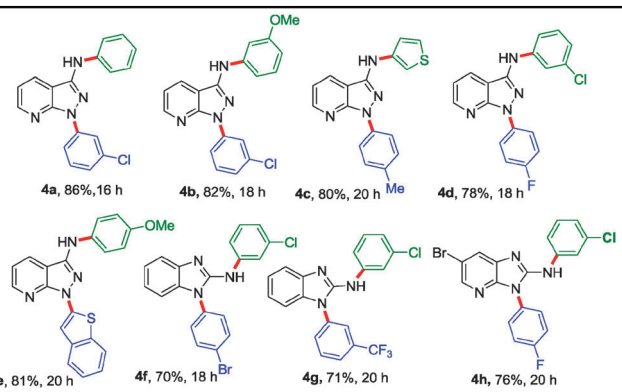
[a] Reaction conditions: N^1-aryl C-NH_2-azoles (1.0 equiv.), phenylboronic acid (1.2 equiv.), $Cu(OAc)_2$ (0.2 equiv.), CsOPiv (0.4 equiv.), DMF (1 mL), 50 °C, air. [b] Isolated yield. [c] $Cu(OAc)_2$ (1 equiv.), Et_3N (3 equiv.). [d] CsOPiv (0.4 equiv.). [e] Reaction performed under a N_2 atmosphere.

With the optimized reaction conditions first we explored the scope of this method with 1-aryl-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine. To our delight, all the electronically diverse boronic acids underwent clean conversion (Table 5) to give desired *C*-NH_2-arylated products (**4a–e**) in excellent yields (78–86%). In this aspect other *C*-amino-*N*-aryl-azole systems were also tested and the resulting *C*-NH_2-arylated products (**4f–h**) isolated in good yields (70–76%).

These two step sequential *N*-arylation protocols can be performed in one-pot under the optimized conditions. The

Table 5 *C*-NH_2-arylation of N^1-aryl-*C*-NH_2-azoles[a]





[a] Reaction conditions: N^1-aryl-*C*-NH_2-azoles (1 equiv.), boronic acid (1.2 equiv.), $Cu(OAc)_2$ (0.2 equiv.), CsOPiv (0.4 equiv.), DMF (1 mL), 50 °C, air, 16–20 h.

isolated yields (**4b** & **4f**) are comparable with the isolated yield obtained in the sequential two steps (for detailed experimental procedures see ESI†).

Several mechanistic studies have been reported for Chan–Lam type of coupling reactions.[9b,15] The coupling product [Ar–azole(Nu)] could be generated by reductive elimination from a copper(III) intermediate [Ar–Cu(III)–Nu].[3a] The presence of O_2(air) here favors this step by *in situ* oxidation of the corresponding [Ar–Cu(II)–Nu] complex.[4d,e,15b] Finally, O_2 (air) acts as a terminal oxidant to regenerate the catalytically active species after the reductive elimination step.[10,15b]

In summary, we have developed two simple and inexpensive systems for copper-catalyzed sequential *N*-arylations of *C*-amino-*NH*-azoles with aryl/heteroaryl boronic acids. Undoubtedly, the success of these sequential/one-pot Cu-catalyzed C–N bond formation reactions further extends the usefulness of Chan–Lam type of coupling with a new substrate class.

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