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Ligand-Free Copper-Catalyzed Amination of Heteroaryl Halides with Alkyl- and Arylamines

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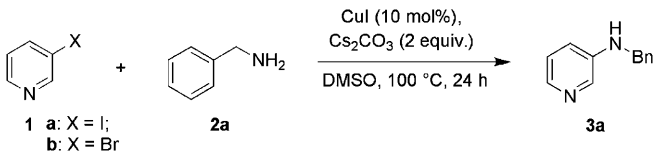
Abstract: *N*-Heteroarylations of alkyl- and arylamines with various heteroaryl halides have been achieved by ligand-free copper-catalyzed cross-couplings affording aminopyridines and aminopyrimidines in moderate to high yields (up to 99% yield).

Keywords: aminopyridines; aminopyrimidines; copper; *N*-heteroarylation; ligand-free conditions

Heteroaromatic compounds are ubiquitous in natural products and biologically active molecules.[1] Among them, aminopyridines and aminopyrimidines are of great interest in the fine chemical industry owing to their importance as intermediates for pharmaceuticals,[2a–e] agrochemicals[2f,g] and materials.[2h–j] Traditional preparations of such compounds involve nucleophilic aromatic substitutions of pyridine or pyrimidine halides, but those methods suffer from a limited substrate scope due to the requirement of activated substrates or harsh reaction conditions.[3] C–N cross-coupling reactions catalyzed by palladium and copper complexes offer an alternative approach to such compounds. Significant progress has been achieved in palladium-catalyzed *N*-heteroarylations of alkyl- and arylamines,[4] but their industrial applications are often problematic due to the high costs of the palladium catalysts and the requirement of air- and moisture-sensitive phosphine ligands. In recent years, copper-catalyzed Ullmann-type reactions have emerged as alternatives.[5] Many efficient copper/ligand combinations have been developed that allow one to perform these reactions under comparatively mild conditions. However, cross-couplings between heteroaryl halides and alkyl- or arylamines have remained challenging,[6] and the development of simple and general copper catalyst systems for efficiently promoting *N*-heteroarylations of alkyl- and arylamines is highly desirable. Recently, we described microwave-accelerated copper-catalyzed aminations of halopyridines with various nitrogen nucleophiles under solvent- and ligand-free conditions.[7] To our disappointment, however, alkyl- and arylamines did not react. In continuation of those studies and in the context of our general search for simple and environmentally friendly catalysts for C–X couplings,[8] we have now discovered a reaction variant that overcame this problem. Hence, the previously unreactive alkyl- and arylamines can now be applied,[9] and the use of ligand-free copper catalysts allows *N*-heteroarylations providing coupling products in moderate to high yields.

While searching for an efficient ligand for the promotion of the copper-catalyzed coupling between 3-iodopyridine (**1a**) with benzylamine (**2a**), we were surprised to find that the reaction proceeded well in the absence of a ligand affording the corresponding coupling product **3a** in 74% yield (Scheme 1).[10]

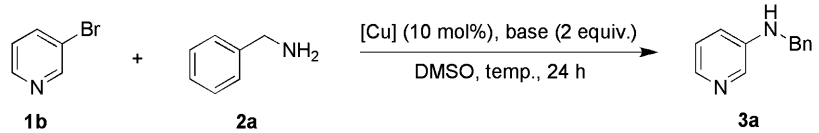
Hence, we turned our attention to the coupling of less reactive and economically more attractive heteroaryl bromides. Unfortunately, the coupling of 3-bromopyridine (**1b**) with benzylamine (**2a**) gave only trace amounts of **3a** when the reaction was carried out under the same reaction conditions as before (10 mol% of CuI and 2 equiv. of Cs_2CO_3, 100 °C,



1 **a**: X = I; **b**: X = Br — **2a** — **3a**

Scheme 1. Ligand-free copper-catalyzed amination of 3-iodopyridine (**1a**) with benzylamine (**2a**).

Table 1. Optimization of the copper-catalyzed coupling reaction of 3-bromopyridine (**1b**) with benzylamine (**2a**).



1b **2a** **3a**

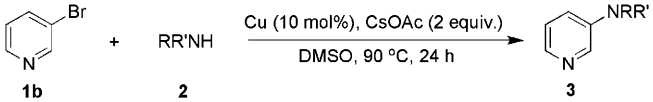
Entry	[Cu]	Base	Temperature [°C]	Yield [%][a]
1	CuI	Cs_2CO_3	100	traces
2	CuI	Cs_2CO_3	120	11
3	CuI	K_3PO_4	100	4
4	CuI	K_2CO_3	100	12
5	CuI	CsOAc	100	>95
6[b]	CuI	CsOAc	100	97
7	CuI	CsOAc	90	>95
8	CuI	CsOAc	80	85
9[c]	CuI	CsOAc	100	67
10	CuI	LiOAc	90	35
11	CuI	NaOAc	90	33
12	CuI	KOAc	90	47
13	CuBr	CsOAc	90	92
14[d]	CuCl	CsOAc	90	90
15	CuOAc	CsOAc	90	> 95
16	Cu_2O	CsOAc	90	93
17	$Cu(OAc)_2 \cdot H_2O$	CsOAc	90	95
18	$CuCl_2$	CsOAc	90	95
19	$CuSO_4 \cdot 5H_2O$	CsOAc	90	90
20	CuO	CsOAc	90	70
21	Cu	CsOAc	90	98
22	–	CsOAc	90	traces

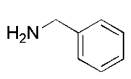
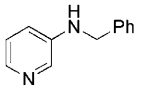
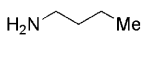
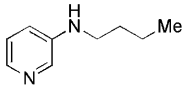
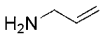
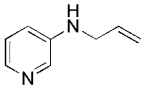
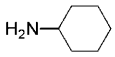
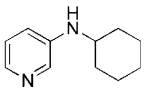
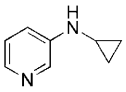
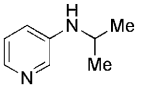
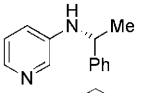
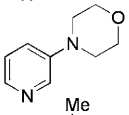
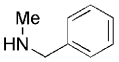
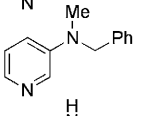
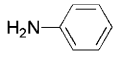
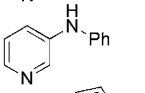
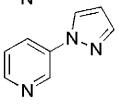
[a] Referring to the amount of product isolated by chromatography.
[b] Under air.
[c] Use of DMF as the solvent instead of DMSO.
[d] Use of 99.995% of CuCl.

Table 1, entry 1). At an elevated temperature an 11% yield of **3a** was obtained (Table 1, entry 2). The choice of base has often been found to be critical in arylamination reactions. Subsequently, the commonly used bases for C–N couplings, such as K_3PO_4 and K_2CO_3, were examined, but lower yields were observed in all cases (Table 1, entries 3 and 4). Surprisingly, when CsOAc[11] was used as the base to promote this transformation, a quantitative yield was obtained (Table 1, entry 5). It is noteworthy that the cross-coupling process proved to be insensitive to oxygen, as evidenced by the fact that the coupling product was also obtained in nearly quantitative yield when the reaction was carried out in air (Table 1, entry 6). Even when the reaction temperature was lowered to 90 °C, a high yield of **3a** was obtained (Table 1, entry 7). DMSO proved to be superior to alternative solvents (Table 1, entries 5, 6 and 9). Other acetate salts, such as LiOAc, NaOAc and KOAc, furnished the coupling product in lower yields ranging from 33–47% (Table 1, entries 10–12). All the copper sources tested, including Cu(I), Cu(II) and Cu(0), catalyzed the coupling reaction, affording **3a** in good to excellent yields (Table 1, entries 7 and 13–21). Copper powder was chosen for further investigations as it is economically most attractive. A blank experiment confirmed that in the absence of the copper catalyst no coupling product was formed (Table 1, entry 22). Hence, the optimal reaction conditions for the ligand-free *N*-heteroarylation of benzylamine (**2a**) with 3-bromopyridine (**1b**) involved the use of 10 mol% of copper powder and 2 equivalents of CsOAc in DMSO at 90 °C (Table 1, entry 21).

Encouraged by the efficiency of the new cross-coupling protocol, the substrate scope was investigated next. As shown in Table 2, all couplings proceeded smoothly and moderate to high yields were obtained. Unbranched aliphatic primary amines proved to be excellent substrates for the coupling with 3-bromopyridine (**1b**), providing the corresponding amination products in high yields (Table 2, entries 1–3). The coupling reactions of sterically hindered α-branched primary amines, such as cyclohexylamine, isopropylamine and 1-phenylethylamine, occurred in good yields as well (entries 4, 6 and 7), although a higher temperature was required for 1-phenylethylamine

Table 2. Ligand-free Cu-catalyzed amination of 3-bromopyridine (**1b**).



Entry	RR'NH	Product		Yield (%)[a]
1			**3a**	98
2			**3b**	98
3			**3c**	94
4			**3d**	81
5[b]			**3e**	42
6[c]			**3f**	70
7[d]			**3g**	82
8			**3h**	63
9[d]			**3i**	44
10[d]			**3j**	53
11			**3k**	48

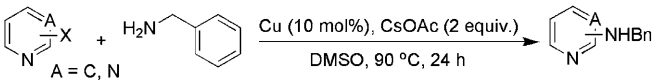
[a] Referring to the amount of product isolated by chromatography.
[b] Use of 3.0 equiv. of amine and CuI instead of Cu.
[c] Use of 5.0 equiv. of amine.
[d] Reaction performed at 110 °C.

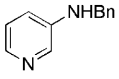
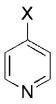
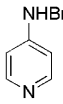
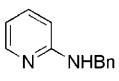
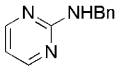
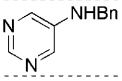
(entry 7). When cyclopropylamine was used as the coupling partner, only a moderate yield was obtained, presumably due to the lability of both cyclopropylamine and the coupling product (entry 5).[12] Furthermore, cyclic and acyclic aliphatic secondary amines, aniline and pyrazole could be coupled with 3-bromopyridine, affording the corresponding products in moderate yields (entries 8–11).

To further evaluate the scope of the process with respect to the heteroaryl halides, a variety of heteroaryl iodides, bromides, chlorides and fluorides were tested under the optimized reaction conditions using benzylamine as model substrate. The results are summarized in Table 3. Both pyridine iodides and bromides, as well as pyrimidine bromides, irrespective of the leaving group in the position of the heteroaromatic ring, afforded the corresponding coupling product in excellent yields (92–99%, Table 3, entries 1 and 2, 5 and 6, 9 and 10, 13 and 15). 3-Chloropyridine and 3-fluoropyridine showed very low reactivity, and the coupling reactions gave less than 10% yield even at higher temperature (entries 3 and 4). The couplings of benzylamine with 4-fluoropyridine hydrochloride and 2-fluoropyridine furnished the products in moderate yields (entries 8 and 12), and probably those reactions involved an S_NAr mechanism. Although low yields were obtained in couplings of 4-chloropyridine hydrochloride (entry 7) and 2-chloropyridine (entry 11), an almost quantitative yield was observed in the coupling with 2-chloropyrimidine (entry 14). Furthermore, 3-bromothiophene also coupled well with **2a** affording the coupling product in a moderate yield (entry 16). Use of 2-bromothiophene as the coupling partner was unsuccessful (entry 17).

In summary, we have developed a simple and versatile, ligand-free copper-catalyzed coupling protocol

Table 3. Ligand-free Cu-catalyzed *N*-heteroarylations of benzylamine (**2a**) with various heteroaryl halides.



Entry	Het-X	Product		Yield [%][a]
1			**3a**	98 (X = I)
2				98 (X = Br)
3[b]				6 (X = Cl)
4[b]				< 10 (X = F)
5			**4**	> 95 (X = I)
6[c]				93 (X = Br)
7[c,d]				22 (X = Cl)
8[c,d]				58 (X = F)
9			**5**	> 95 (X = I)
10				92 (X = Br)
11[d]				30 (X = Cl)
12[d]				50 (X = F)
13			**6**	91 (X = Br)
14[d]				98 (X = Cl)
15			**7**	> 95
16			**8**	56
17			**9**	traces

[a] Referring to the amount of product isolated by chromatography.
[b] Reaction performed at 120 °C.
[c] Starting from the hydrochloride of the halopyridine.
[d] Reaction performed at 110 °C.

for alkyl- and arylamines with various heteroaryl halides. The procedure is insensitive to air and moisture, which makes it more attractive for an industrial application than the related Pd-catalyzed reactions. The method described here also complements our previous reports[7,8] and greatly expands the substrate scope. Further studies to find more efficient catalyst systems and to continue expanding the substrate scope are currently in progress in our laboratories.

Experimental Section

General Procedure for *N*-Heteroarylations of Nitrogen Nucleophiles [Example: Synthesis of *N*-Benzylpyridin-3-amine (3a)]

After cooling of an oven-dried tube to room temperature under argon, it was charged with copper powder (3.3 mg, 0.05 mmol) and CsOAc (196 mg, 1.0 mmol). 3-Bromopyridine (**1b**, 50 μL, 0.5 mmol) and benzylamine (**2a**, 84 μL, 0.75 mmol) were added followed by dry DMSO (0.5 mL). The tube was sealed and the mixture was heated to 90 °C. After stirring at this temperature for 24 h, the heterogeneous mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). The resulting solution was filtered through a pad of silica gel and concentrated to give the crude product. Purification by silica gel chromatography (1:1 pentane/ethyl acetate) gave *N*-benzylpyridin-3-amine (**3a)** as a white solid; yield: 91 mg (98%). The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis. See the Supporting Information for full details.

Acknowledgements

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