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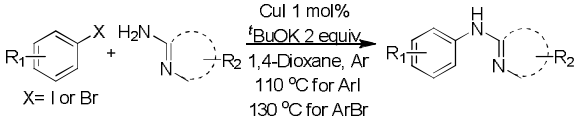

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Ligand Free Copper-Catalysed N-Arylation of Heteroarylamines

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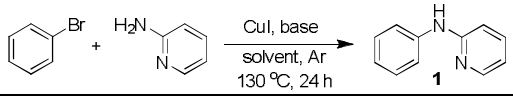
ABSTRACT

An efficient protocol for ligand-free Cu-catalyzed N-arylation of heteroarylamines has been developed. With the use of 1% CuI, a wide range of aryl iodides and bromides coupled with heteroarylamines to afford the corresponding products in high yields. Further, this protocol is particularly suitable for the reactions of the most hindered aryl iodides with 2-aminopyridines.

Cu-catalyzed C-N bond-forming protocols are broadly considered as convenient and practical tools for assembling N-arylation products.[1] With the use of various kinds of additional ligands,[2-10] several classes of amine derivatives, including aliphatic amine, anilines, amides, and N-Aryl heterocycles, underwent N-arylation process successfully under considerably mild conditions. However, due to the poor nucleophilicity of the amine nitrogen atom caused by the neighbouring heteroatom, heteroarylamines have historically been challenging substrates for Cu-catalyzed N-arylation.[11] Although several protocols for the copper-catalyzed N-arylation of these heteroarylamines have been reported,[12] but they usually require high Cu loadings, additional ligands, and the use of an activated aryl electrophile such as boronic acids. For example, the most realizable approach for the coupling of aryl halides with heteroarylamines to date was reported by Liu,[12c] in which 25-100% Cu and DMEDA are essential for the formation of heteroaryl diarylamines in moderate to good yields. In order for the coupling of aryl bromides to take place efficiently, 200% potassium iodide were also used to effect an in situ halide exchange reaction.[13] In contrast to its problematic synthesis, however, N-arylheteroarylamines have emerged as an important class of motifs in a range pharmaceuticals, notably protein kinase inhibitors such as STI571 (Imatinib or Gleevec)[14] and BMS354825 (Dasatinib).[15] Thus, a simple and efficient route for the synthesis of N-arylheteroarylamines remains highly desirable. Herein, we wish to disclose a highly efficient N-arylation of heteroarylamines using 1% CuI as catalyst without any additional ligands.

Initially, we selected the coupling of PhBr with 2-amino-pyridine as a model to optimize the reaction conditions, and the results were summarized in Table 1. Of the bases and solvents

Table 1
Optimization of the reaction conditions.[a]



Entry	Base	Solvent	Yield (%)
1	K_2CO_3	Toluene	0
2	KOH	Toluene	0
3	NaOEt	Toluene	23
4	NaO^{t}Bu	Toluene	57
5	KO^{t}Bu	Toluene	76
6	KO^{t}Bu	Dioxane	93
7	KO^{t}Bu	DMSO	51
8	KO^{t}Bu	DMF	<5
9	KO^{t}Bu	^{t}BuOH	<5
10	KO^{t}Bu	Dioxane	92[b]
11	KO^{t}Bu	Dioxane	<5[c]

[a] Unless otherwise noted, reactions were conducted with aryl bromide 1.0 mmol, 2-aminopyridine 1.5 mmol, CuI 5 mol%, base 2.0 mmol, solvent 1.0 mL, at 130 °C under argon for 24 h.

[b] 1 mol% CuI.

[c] Without CuI.

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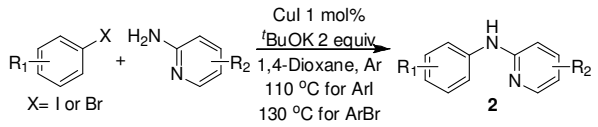
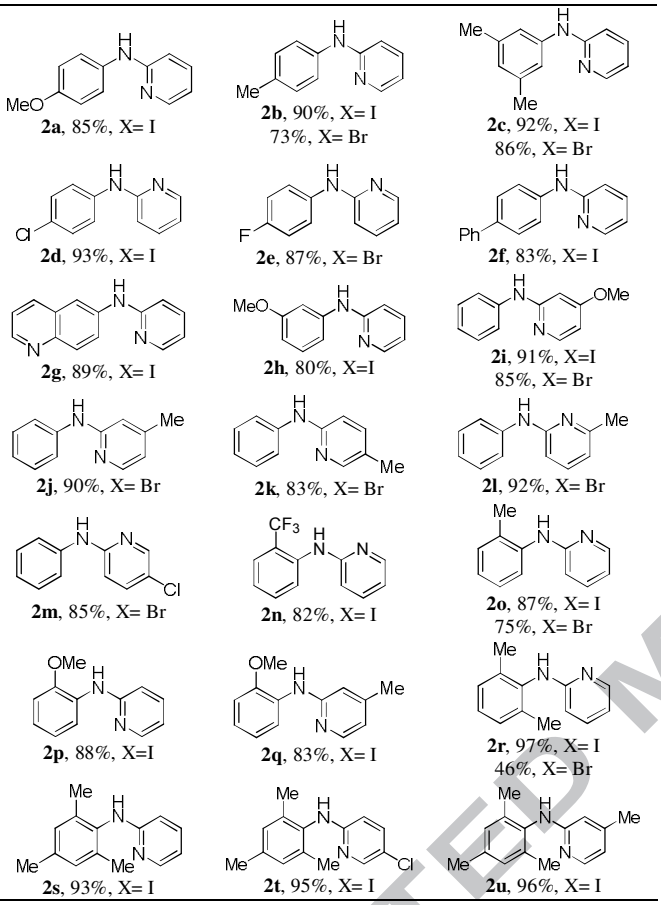
Table 2

Copper-catalyzed N-arylation of 2-aminopyridine.[a]





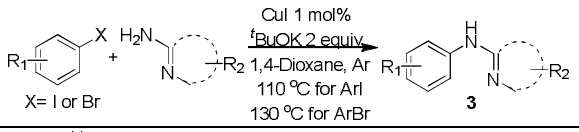
[a] Unless otherwise noted, reactions were conducted with aryl halides 1.0 mmol, 2-aminopyridine 1.5 mmol, CuI 1 mol%, KO^{t}Bu 2.0 mmol, dioxane 1.0 mL, at 110 °C (X= I) or 130 °C (X= Br) under argon for 24 h.

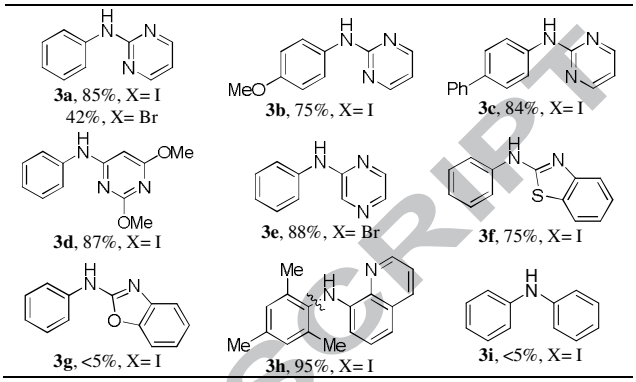
screened, KO^{t}Bu as the base and dioxane as the solvent proved to be the most effective combination for this Cu-catalyzed reaction (Table 1, entry 6). Additionally, we were pleased to find that an excellent yield (92%) was obtained even reducing Cu loadings to 1% (Table 1, entry 9). But no desired product was isolated without the use of CuI (Table 1, entry 11).

Having the optimal conditions in hand, we set out to investigate the scope of the coupling reaction. As shown in Table 2, a variety of aryl iodides (at 110 °C) and bromides coupled with 2-aminopyridine to afford the corresponding products in good yields (**2a-h**). Heterocyclic aryl iodide was also well compatible (**2g**). Subsequently, a range substituted 2-aminopyridines were evaluated under the same reaction conditions. Kinds of 2-aminopyridines substituted in different positions could be arylated under the catalyst of 1% CuI with high yields (**2i-m**). It is worth mentioning that hindered, *ortho*-substituted aryl halides also reacted with 2-aminopyridine in good yields (Table 2, **2n-u**). For example, 1-iodo-2-methylbenzene, a less hindered iodoarene, coupled with 2-aminopyridine to give the desired product in 87% yield in the presence of 1 mol% CuI, for the reaction of 1-bromo-2- methylbenzene, a slightly low

Table 3

Scope of 2-Aminopyridine-like Nucleophiles.[a]





[a] Unless otherwise noted, reactions were conducted with aryl halides 1.0 mmol, 2-aminopyridine 1.5 mmol, CuI 1 mol%, KO^{t}Bu 2.0 mmol, dioxane 1.0 mL, at 110 °C (X= I) or 130 °C (X= Br) under argon for 24 h.

yield (75%) was obtained. Moreover, 2,6-disubstituted aryl iodides, the most hindered halogenoarenes which have been considered as a class of historical problematic substitutes for Cu-catalyzed coupling reactions, coupled with 2-aminopyridine successfully in excellent yields (Table 2, **2r-u**). In addition, the reaction of 2,6-dimethyl aryl bromide with 2-aminopyridine occurred only in a moderate yield (46%) (Table 2, **2r**).

Next, we were interested in exploring the generality of these conditions for the reaction of a range 2-aminopyridine-like nucleophiles. 2-Aminopyrimidine (Table 3, **3a-c**), substituted 4-aminopyrimidine (**3d**), as well as 2-aminopyrazine (**3e**), could all be arylated in good yields using the optimal conditions (although the arylation process with aryl bromide to provide **3a** in a lower yield). Furthermore, the reaction of 2-aminobenzothiazole with iodobenzene proceeded well and afforded the corresponding N-arylated products in a yield of 75% (**3f**), but the arylation of 2-aminobenzoxazole was not successful (**3g**). Interestingly, we found that the above conditions were inefficient for the arylation of aminobenzene (**3i**) but were highly effective for the arylation of 8-aminoquinoline even using a most hindered aryl iodide as the coupling partner (**3h**). This might be due to the chelating interaction of aminobenzene with copper ion not to form a ring, but the chelating interaction of 8-aminoquinoline with copper ion to form a transitional 5-member ring, which may efficiently facilitate the coupling reaction.

In conclusion, a general method for the Cu-catalyzed N-arylation of heteroarylamines with aryl iodides and bromides has been disclosed. With the use of only 1% CuI, the arylation processes occur in high yields without additional ligands. Notably, this protocol is very suitable for the coupling reaction between the most hindered aryl iodides and 2-aminopyridine.

Acknowledgments

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