

An Inexpensive and Efficient Copper Catalyst for *N*-Arylation of Amines, Amides and Nitrogen-Containing Heterocycles

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Abstract: An inexpensive and efficient catalyst system has been developed for the *N*-arylation of nitrogen-containing compounds including a variety of amines, amides, indole and imidazole. This simple protocol uses CuI as the catalyst, commercial avail-

able pipecolic acid as the new ligand, K₂CO₃ as the base and DMF as the solvent.

Keywords: arylation; copper; cross-coupling; homogeneous catalysis; N,O ligands

Introduction

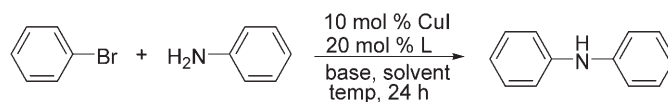
The transition metal-catalyzed formation of carbon-nitrogen bonds *via* cross-coupling reactions plays an important role in the preparation of numerous important products in biological, pharmaceutical and material sciences.^[1] Both the Ullmann reaction (copper-catalyzed *N*-arylation of amines)^[2] and the related Goldberg reaction (copper-catalyzed *N*-arylation of amides)^[3] are traditional methods to assemble these compounds. For a long time, high reaction temperatures, stoichiometric amounts of copper reagents and low toleration of functional groups prevented further development of these methods.^[4a] Although some significant achievements in the palladium-catalyzed *N*-arylation of amines/amides have been made,^[4] the drawbacks of the catalyst systems, such as air sensitivity, high cost and toxicity, limit their applications. During the past years, great progress on the modified Ullmann and Goldberg coupling reactions has been made,^[5] which relied on the utilization of some special bidentate additives such as aliphatic diamines,^[6] 1,10-phenanthroline and its derivatives,^[7] ethylene glycol,^[8a] diethylsalicylamide,^[8b] amino acids,^[9] oxime-type and Schiff base ligands,^[10] thiophene-2-carboxylate,^[11] bidentate phosphines,^[12] diphosphinidenecyclobutene,^[13] diphenyl pyrrolidine-2-phosphonate^[14] and pyrrolidine-2-phosphonic acid phenyl monoester.^[15] In this paper, we report a commercially available and efficient bidentate ligand, pipecolic acid, for the copper-catalyzed *N*-arylation of nitrogen-containing

compounds including a variety of amines, amides, indole and imidazole.

Results and Discussion

We first chose aniline and bromobenzene as the model substrates to optimize the catalysis conditions, including the copper sources, bases, solvents, amount of catalyst (CuI) and the ligand (pipecolic acid), as well as reaction temperature, in order to achieve the best results in the Ullmann cross-coupling reactions (Table 1). The experimental results showed that the catalyst system containing 10 mol % CuI and 20 mol % ligand relative to aniline in DMF in the presence of 2 equivs. of K₂CO₃ was highly efficient, and 110 °C as reaction temperature could provide high yield. However, no *N*-arylation product was obtained in the absence of the ligand, which showed that the ligand could promote the *N*-arylation of amine. Under our optimal conditions, the standard ligands, proline^[9i] and *N,N,N',N'*-tetramethylethylenediamine,^[6] gave 68 and 62 % yields, respectively, so the results above show that pipecolic acid also is a good ligand of the copper catalyst.

The coupling reactions of aryl halides with various amines were carried out under our standard reaction conditions. As shown in Table 2, the desired amination products of aryl bromides and iodides were obtained in good to excellent yields (entries 1–9 and 11–18), while the coupling reactions for aryl chlorides

Table 1. Effect of base, solvent and reaction temperature on the coupling of aniline and bromobenzene.^[a]

Entry	Ligand	Base	Solvent	Temp [°C]	Yield [%] ^[b]
1		K ₂ CO ₃	DMF	110	72
2		K ₃ PO ₄	DMF	110	30
3		Cs ₂ CO ₃	DMF	110	72
4		K ₂ CO ₃	DMSO	110	71
5		K ₂ CO ₃	DMF	90	37
6		K ₂ CO ₃	DMF	60	0
7		K ₂ CO ₃	DMF	30	0
8		K ₂ CO ₃	DMF	110	68
9		K ₂ CO ₃	DMF	110	62

^[a] Reaction conditions: bromobenzene (2 mmol), aniline (3 mmol), catalyst (0.2 mmol), ligand (0.4 mmol), solvent (3.0 mL) under N₂.

^[b] Isolated yield.

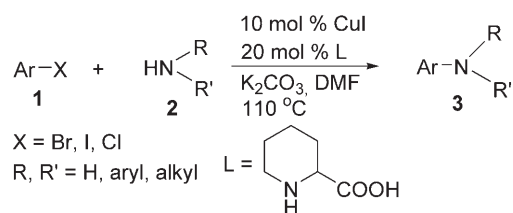
provided low yields (entries 19–22). Aryl iodides showed a higher reactivity than aryl bromides in the coupling reactions. For example, the coupling reaction of 1-bromo-4-iodobenzene with 2-nitroaniline (entry 18) yielded the target product **3p** containing bromine on the benzene ring. The results in Table 2 indicate that the reactivity order of the aryl halides is iodides > bromides > chlorides. Aryl bromides containing electron-donating groups provided slightly low yields (compare entries 3 and 8, 7 and 12).

Aliphatic amines are good substrates (entries 1, 7, 12 and 13 in Table 2). The steric hindrance of arylamines also gave satisfactory results, and the desired *N*-arylation products for arylamines containing a substituent group at the *ortho* site were obtained in slightly lower yields (entries 5, 6, 14, 15 and 16 in Table 2). Interestingly, the coupling reactions of 2-nitroaniline with aryl halides all gave excellent yields (entries 4, 9 and 18). The reaction of 2-nitroaniline with 4-bromoanisole yielded monoarylation and dia-

rylation products (entry 10 in Table 2), and the coupling of 4-nitroaniline with 4-bromoanisole led to 76% of the diarylation product (entry 11 in Table 2).

Encouraged by the promising results of the cross-coupling reactions of aryl halides with amines, we broadened the scope of substrates, and the *N*-arylations of amides, indole, and imidazole were also carried out under our standard reaction conditions. As shown in Table 3, aryl iodides are excellent substrates (entries 2, 5 and 6), and aryl chlorides showed low reactivity (entries 10 and 11). The coupling reactions of 1-bromo-4-iodobenzene with indole and imidazole yielded *N*-arylation products containing a bromine atom (entries 6 and 9).

The mechanism of the pipicolinic acid-promoted copper-catalyzed coupling reactions could be similar to that of amino acid-promoted copper catalysis.^[9] Reaction of pipicolinic acid with CuI produced a five-membered chelate **I**, and the subsequent oxidative addition of the chelate with aryl halide led to the

Table 2. Coupling of aryl halides with various amines.^[a]

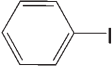
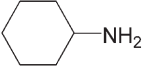
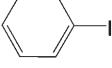
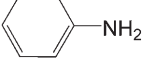
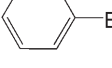
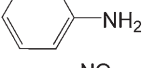
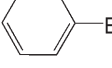
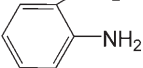
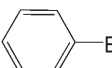
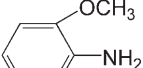
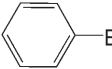
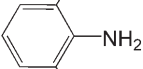
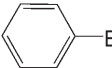
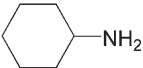
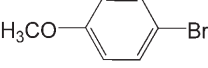
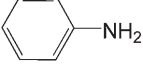
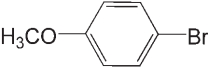
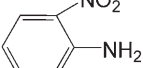
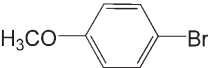
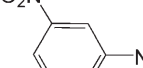
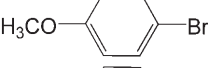
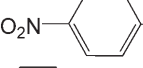
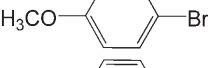
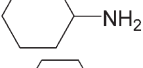
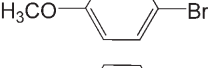
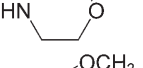
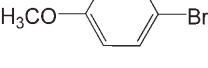
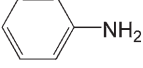
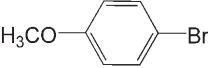
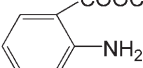
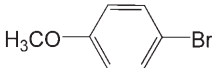
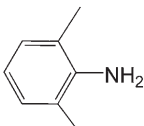
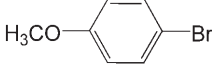
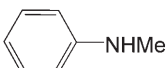
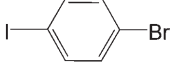
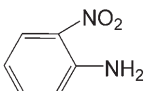
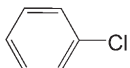
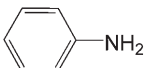
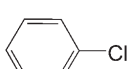
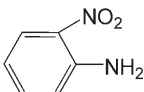
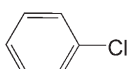
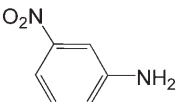
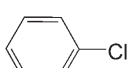
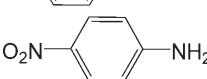
Entry	Aryl halide	RR'NH	Product	Time [h]	Yield [%] ^[b]
1			3a	20	93
2			3b	20	79
3			3b	24	72
4			3c	24	87
5			3d	36	76
6			3e	36	60
7			3a	24	86
8			3f	24	67
9			3g	24	80
10			3h 3h'	24	29 ^[c] 23 ^[d]
11			3i	24	76 ^[d]
12			3j	20	81
13			3k	20	86
14			3l	36	73
15			3m	20	75

Table 2. (Continued)

Entry	Aryl halide	RR'NH	Product	Time [h]	Yield [%] ^[b]
16			3n	36	66
17			3o	36	57
18			3p	24	93
19			3b	36	15
20			3c	36	31
21			3q	36	25
22			3r	36	27

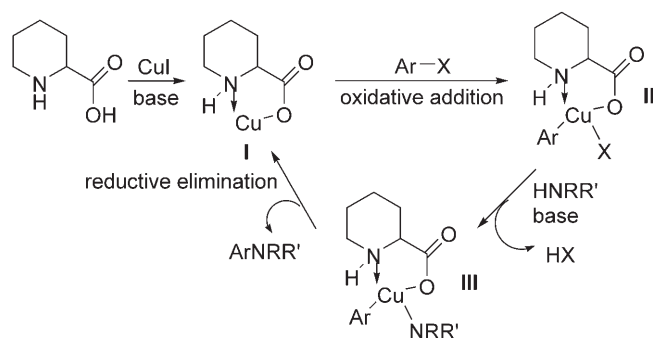
^[a] Reaction conditions: CuI (0.2 mmol), ligand (0.4 mmol), K₂CO₃ (4 mmol) in DMF (3 mL) under N₂; aryl halide (2 mmol), amine (3 mmol).

^[b] Isolated yield.

^[c] *N*-Monoarylation product.

^[d] *N*-Diarylation product.

intermediate **II**. Treatment of amine with **II** in the presence of the base potassium carbonate provided the complex **III**, and then reductive elimination of **III** gave the *N*-arylation product and the chelate **I** (Scheme 1). The mechanism could explain the reactivity order of aryl halides, ArI > ArBr > ArCl, and the affect of substituent groups on the aryl rings of the aryl halides: electron-withdrawing group > electron-donating group.



Scheme 1. Possible mechanism of the copper-catalyzed *N*-arylation reaction.

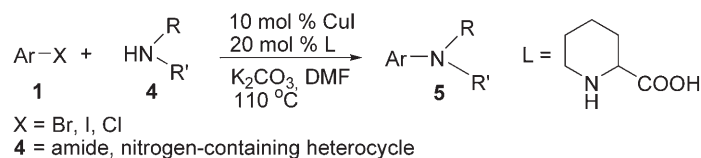
Conclusions

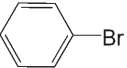

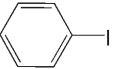

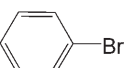

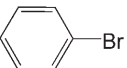
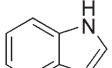
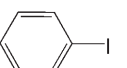
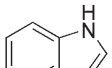
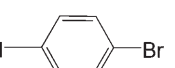
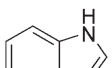
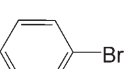

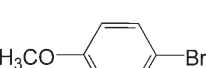

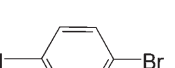

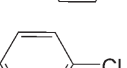
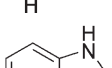
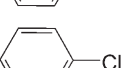

We have developed a general and efficient protocol for the *N*-arylation of aromatic amines, aliphatic amines, amides, indole and imidazole. The CuI-catalyzed Ullmann and Goldberg coupling reactions were promoted by the new bidentate ligand, pipecolinic acid, which is commercially available and inexpensive. The catalyst system can be widely used for the *N*-arylation of nitrogen-containing compounds.

Experimental Section

General Procedure for the Preparation of Compounds **3** and **5**

A flask was charged with CuI (38 mg, 0.2 mmol), pipecolinic acid (52 mg, 0.4 mmol) and potassium carbonate (552 mg, 4 mmol), evacuated and backfilled with nitrogen at room temperature. Aryl halide (2 mmol), amine (3 mmol), and DMF (3 mL) were added to the flask under a nitrogen atmosphere. The flask was immersed in an oil bath, and the reaction mixture was stirred at the indicated temperature for the corresponding reaction time (see Table 2 and Table 3). The reaction mixture was cooled to room tempera-

Table 3. Coupling of aryl halides with amides, indole, imidazole.^[a]

Entry	Aryl halide	RR'NH	Product	Time [h]	Yield [%] ^[b]
1			5a	36	78
2			5a	36	86
3			5b	36	70
4			5c	24	91
5			5c	24	95
6			5d	24	94 ^[c]
7			5e	24	76
8			5f	24	71
9			5g	24	84 ^[d]
10			5c	24	36
11			5a	30	24

^[a] Reaction conditions: CuI (0.2 mmol), ligand (0.4 mmol), K₂CO₃ (4 mmol) in DMF (3 mL) under N₂; aryl halide (2 mmol), amine (3 mmol).

^[b] Isolated yield.

^[c] Product: *N*-(*p*-bromophenyl)indole.

^[d] Product: *N*-(*p*-bromophenyl)imidazole.

ture, 20 mL of ethyl acetate were added, and the resulting suspension was filtered. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane-EtOAc=40:1 to 6:1) to provide the desired product.

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