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Copper(I)-picolinic acid catalyzed N-arylation of hydrazides

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ABSTRACT

An efficient copper-catalyzed carbon–nitrogen bond formation is described. The copper(I) complex with commercially available 2-picolinic acid ligand was found to be effective in N-arylation of *N*-Boc-hydrazine. This methodology offers a regioselective N-arylation of hydrazides using a variety of substituted aryl iodides.

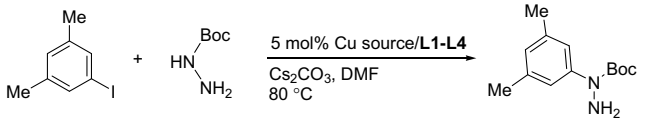
1. Introduction

Transition metal catalyzed cross-coupling methodology is one of the most powerful tools for bond construction between organometallic nucleophiles and electrophiles.[1] Palladium complex with phosphine ligand is always an effective catalyst system in these reactions.[2] However, the expensiveness of the precious metal source as well as the supporting ligands sometimes limits their versatility and applicability in industrial processes. In view of this shortcoming, considerable efforts in searching inexpensive catalytic system are continuing. Recently, significant advances have been made on the evolution of relatively less expensive copper-catalyzed Ullmann-type reactions.[3] With the application of structurally appropriate ligands (such as *N,N,N,O,* or *O,O*-bidentate ligands), numerous Cu-catalyzed C–N,[4] C–O,[5] C–S,[6] and C–C[7] coupling reactions could be carried out under relatively mild reaction conditions.

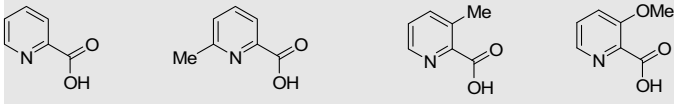
We recently reported an effective copper catalyst system for the arylation of malonates.[8] This versatile copper(I)-picolinic acid complex showed effective C–C coupling even at room temperature reaction conditions. There are a number of successful Cu-catalyzed N-arylations that have been reported, however, the examples on regioselective N-arylation of hydrazine derivatives are rare.[9] In 2001, Buchwald and co-workers reported Cu–phen complex catalyzed N-arylation of hydrazides.[9a] They also briefly showed the application of Cu–picolinic acid system in some selected examples. Nevertheless, room for exploration of efficient catalytic system remains. Herein, we report our Cu–picolinic acid system to the relatively unexplored Cu-catalyzed N-arylation of hydrazides.

Initial screenings of the C–N bond formation between *N*-Boc-hydrazide and aryl iodide were triggered as a function of copper source and picolinic acid ligand derivatives (Table 1). Control experiment revealed that nearly no conversion of aryl iodide was observed in the absence of ligand (entry 1). Copper bronze essentially gave no conversion of aryl iodides while CuCl, CuOTf and $Cu(MeCN)_4ClO_4$ complexes were not as efficient as the CuI (entries 2–6). In addition to the metal sources, we examined the coordination efficiency of the 2-picolinic acid scaffold to the copper metal sphere. Ligand **L2** with a substituted methyl group on the 6-position presumably hindered the coordination of the nitrogen

Table 1
Initial screening of copper source and picolinic acid ligand derivatives in Cu-catalyzed N-arylation of hydrazide[a]



Entry	Copper source	Ligand	Yield[b]
1	CuI	No ligand	Trace
2	CuI	**L1**	65
3	CuCl	**L1**	51
4	Cu powder (bronze)	**L1**	Trace
5	CuOTf	**L1**	63
6	$Cu(MeCN)_4ClO_4$	**L1**	53
7	CuI	**L2**	31
8	CuI	**L3**	34
9	CuI	**L4**	39



L1 **L2** **L3** **L4**

[a] 5-Iodo-*m*-xylene (1.0 mmol), *tert*-butylcarbazate (1.2 mmol), Cu source (5 mol %), ligands **L1–L4** (10 mol %), Cs_2CO_3 (3.0 mmol), and DMF (1.0 mL) under N_2 at 80 °C for 24 h.
[b] Isolated yields were reported.

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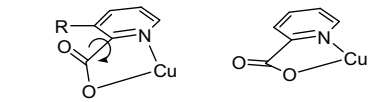


Figure 1. Suggested binding modes for the picolinic acid ligands.

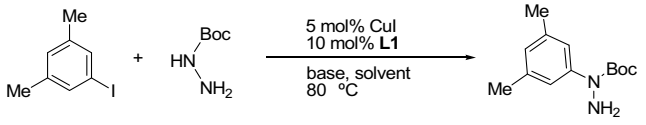
atom to the metal center, and hence catalytic efficacy was lowered (entry 7). Upon placing either a methyl or a methoxy group to the 3-position of the ligand (i.e., **L3** and **L4**), lower catalytic activities were observed (entries 8–9). It is suggested that the 2-picolinic acid **L1** could offer a suitable planar *N,O* coordination, while the **L3** and **L4** might not provide effective binding templates (Fig. 1).

Several types of bases were investigated in order to seek the best reaction conditions (Table 2). Cesium carbonate gave the desired product in the highest yield among other commonly used inorganic bases (entries 1 vs 4–8). Moreover, 3 equivalents of the base was found to be optimal (entries 1–3). Apart from the base screening, solvent parameter was examined. DMF provided the highest efficiency while dioxane, THF, *tert*-amyl alcohol, and toluene gave moderate yields (entries 1, 9–12).

In order to probe the effectiveness of this Cu-catalyzed protocol, a series of aryl iodides were examined (Table 3). A variety of *para*- and *meta*-substituted aryl iodides with functional groups such as chloro, methoxy, trifluoromethyl, amino, cyano, and hydroxyl were compatible under our reaction conditions (entries 3–10). Interestingly, there was no competitive N-arylation of aniline in this reaction when 4-iodoaniline was used (entry 7). No significant electronic effect to the rate or yield of the reaction was observed. Heterocycle such as 3-iodopyridine furnished the desired product in moderate yield (entry 11). Presumably, the nitrogen atom from this electrophile exerts competitive coordination to the copper sphere, and renders the complex coordinatively saturated. Although some functionalized aryl iodides could tolerate the present reaction conditions, the phenolic, ester, nitro and thienyl groups were found to be inferior (Fig. 2).

In summary, coupling with our previous investigation using Cu–picolinic acid catalyst, we have extended the scope of this simple system to the underdeveloped N-arylation of hydrazine derivatives. The inexpensiveness and commercial availability of the Cu source as well as the 2-picolinic acid ligand offer attractive features

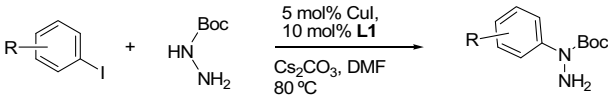
Table 2
Base and solvent optimization for Cu-catalyzed N-arylation of hydrazide[a]

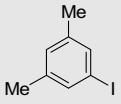
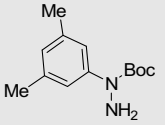
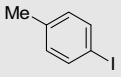
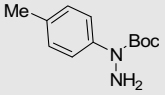
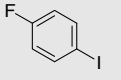
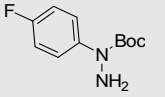
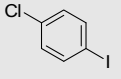
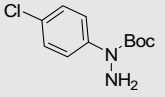
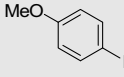
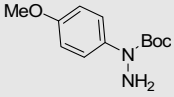
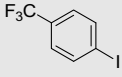
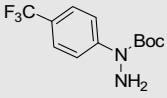
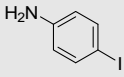
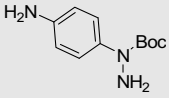
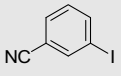
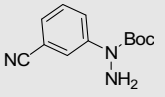
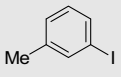
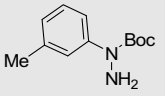
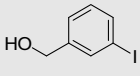
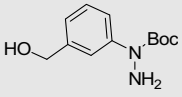
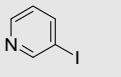
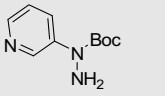
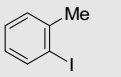
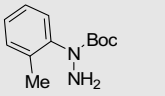


Entry	Base (equiv)	Solvent	Yield[b]
1	Cs_2CO_3 (3.0)	DMF	70
2	Cs_2CO_3 (1.5)	DMF	12
3	Cs_2CO_3 (6.0)	DMF	48
4	Li_2CO_3 (3.0)	DMF	15
5	K_2CO_3 (3.0)	DMF	11
6	Na_2CO_3 (3.0)	DMF	Trace
7	K_3PO_4 (3.0)	DMF	Trace
8	NaO*t*-Bu (3.0)	DMF	Trace
9	Cs_2CO_3 (3.0)	Dioxane	40
10	Cs_2CO_3 (3.0)	*t*-Amyl alcohol	58
11	Cs_2CO_3 (3.0)	THF	43
12	Cs_2CO_3 (3.0)	Toluene	49

[a] 5-Iodo-*m*-xylene (1.0 mmol), *tert*-butylcarbazate (1.2 mmol), CuI (5 mol %), ligand **L1** (10 mol %), base (1.5–6.0 mmol), and solvent (1.0 mL) under N_2 at 80 °C for 24 h.
[b] Isolated yields were reported.

Table 3
Copper-catalyzed coupling of aryl iodides with *N*-Boc-hydrazine[a]



Entry	Arl	Product	Isolated yield
1			73
2			67
3			65
4			65
5			61
6			67
7			62
8			52
9			70
10			30
11			52
12			28

[a] Aryl iodide (1.0 mmol), *tert*-butylcarbazate (1.2 mmol), CuI (5 mol %), ligand **L1** (10 mol %), Cs_2CO_3 (3.0 mmol), and DMF (1.0 mL) under N_2 at 80 °C for 24 h.

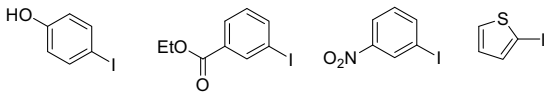


Figure 2. Unsuccessful examples for the Cu-catalyzed N-arylation of hydrazine derivative.

to this protocol. Further investigations of this versatile catalytic system will be reported in due course.

2. Experimental

2.1. General consideration

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. DMF was predried by calcium hydride, and distillated under reduced pressure. Toluene was distilled from sodium benzophenone ketyl under nitrogen. Commercially available aryl iodides (liquid form only) were purified by passing through a short plug (0.5 cm width × 4 cm height) of neutral alumina or by distillation under reduced pressure. GC analysis was conducted on a HP G1800C GCD system using a HP5MS column (30 m × 0.25 mm). Known products were characterized by NMR and mass spectroscopy and compared to the literature data or authentic sample analysis.

2.2. General procedure

An oven-dried resealable vial was charged with CuI (9.5 mg, 0.05 mmol, 5 mol %), 2-picolinic acid (13.5 mg, 0.10 mmol, 10 mol %), and Cs_2CO_3 (977 mg, 3.0 mmol). The flask was evacuated and backfilled with nitrogen (3 cycles). *tert*-Butylcarbazate (159 mg, 1.2 mmol), aryl iodide (1.0 mmol), and DMF (1.0 mL) were added under nitrogen. The vial was sealed, and the reaction mixture was stirred at 80 °C for 24 h. The resulting suspension was cooled to room temperature, and filtered through a 0.5 × 1 cm silica pad. The crude mixture was purified by column chromatography on silica gel (230–400 mesh).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.050.

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