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Copper-catalyzed amination of aryl halides with nitrogen-containing heterocycle using hippuric acid as the new ligand

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Abstract

An efficient copper-catalyzed amination of nitrogen-containing heterocycles with various aryl halides has been developed. Commercially available and inexpensive hippuric acid is a novel ligand to afford the coupling products in moderate to excellent yields.

1. Introduction

Transition metal catalyzed formation of C–N bonds via cross-coupling reactions represents one of the powerful means for the preparation of numerous important products in pharmaceutical industry and material science.[1] In the past decades, much attention has been attracted on palladium-catalyzed arylation of amines.[2] However, the drawbacks of Pd-catalyst systems, such as high cost and toxicity, limit their massive applications for industrial scales. Thus, the use of a cheaper metal instead of Pd provides an attractive alternative. Copper-based C–N coupling reactions are particularly attractive, due to the low price and environmental friendliness.[3] Recently, various ligands, such as 1,10-phenanthroline,[4] 8-hydroxyquinoline,[5] *trans*-1,2-cyclohexadiamine,[6] ethylene glycol,[7] aminoarenethiolate,[8] amino acids,[9] mono- or bidentate phosphines,[10] and other ligands[11] have been developed for the mild copper-catalyzed aminations of *N*-containing heterocycles. Differently, we[12] and other group[13] have developed copper-catalyzed N-arylations using readily available *rac*-BINOL as a ligand. However, relative little progress[14,15] has been made for the coupling of imidazoles, which are an important class of compounds in medical, biological, and *N*-heterocyclic carbene chemistry.[16] Furthermore, majority of these coupling reactions that has been published are limited to aryl iodides till now.[6a,17] There are two factors that hamper applications including the cost and the availability of the catalysts, particularly the ligand, which is often prepared by tedious synthetic methods. Therefore, to find more efficient and readily available ligands for C–N coupling with broad variety of the substrates is still desirable. In this paper, we wish to report our findings in which the low-cost and air-stable hippuric acid together with air-stable $Cu(OAc)_2 \cdot H_2O$ is an efficient catalyst for the C–N coupling reaction of imidazoles and other heterocycles with aryl iodides, bromides, and chlorides.

2. Results and discussion

In order to explore copper catalysts for the C–N coupling reactions, the coupling of iodobenzene with morpholine was chosen as the model reaction to study the efficiency of a series of readily available ligands (**A**–**E**), 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) (**A**), urotropine (**B**), hexamethylphosphorous triamide (HMPT) (**C**), 2,2-(diacetamido)propionic acid (**D**), and hippuric acid (**E**). As shown in Figure 1, **E** gave the best result (31% yield). Encouraged by this finding, the optimal catalytic conditions were screened. The results are listed in Table 1. The control experiment showed that the coupling reaction performed in the air gave no product (Table 1, entry 2).

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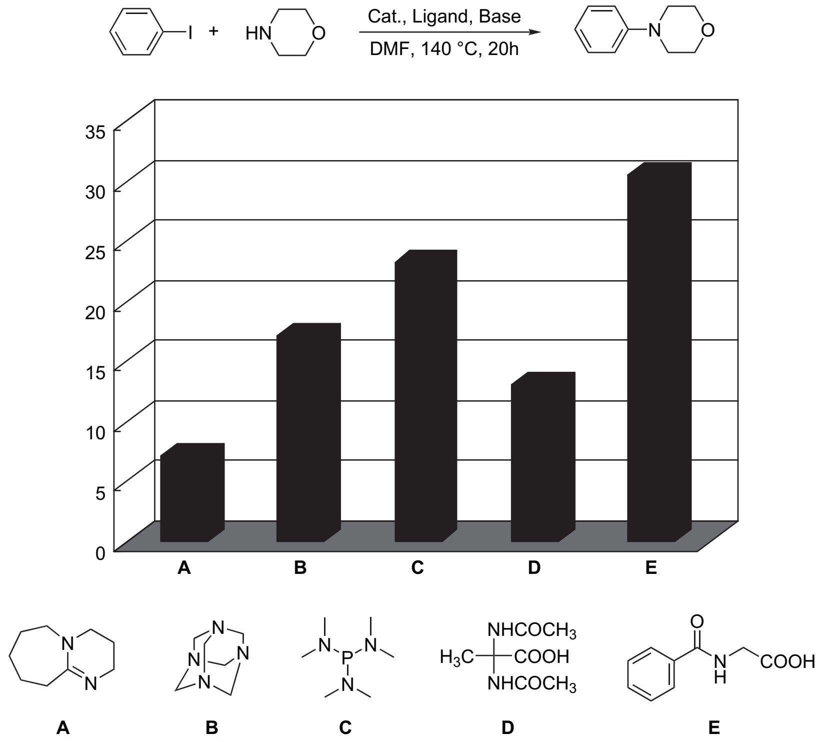


Figure 1. Copper-catalyzed arylation of morpholine promoted by ligands (**A**–**E**).

Furthermore, various widely used inorganic bases such as Cs_2CO_3, K_2CO_3, K_3PO_4, KOH, and KF had remarkable effect on the coupling reactions (entries 1–6), and Cs_2CO_3 was the best among the bases. In addition, organic base such as pyridine was also employed, but gave no corresponding product (entry 7). Subsequently, several readily available copper compounds, such as copper powder and $Cu(OAc)_2 \cdot H_2O$, were investigated for the Ullmann coupling reaction (entries 8–9). To our delight, the air-stable and inexpensive $Cu(OAc)_2 \cdot H_2O$ gave the best result. At the same time, the experimental results suggested that DMF was the best solvent among the screened ones, such as DMSO, THF, and Toluene. Various phase transfer catalysts (PTC) including TBAC (tetrabutyl ammonium chloride), TBAB (tetrabutyl ammonium bromide), and CTAB (cetyl trimethyl ammonium bromide) were employed as additives for the coupling reaction. However, additives have no positive effect on the catalytic reactions (entries 10–12). The effect of the amount of copper salt and the ligand was also studied (entries 13–18). No desired coupling products were obtained in the absence of the ligand (**E**), which showed that the addition of the ligand could promote the C–N coupling reactions. Further experiments indicated that the catalyst system containing 20 mol % of $Cu(OAc)_2 \cdot H_2O$ and 20 mol % of ligand was the optimal choice (entry 15). In addition, replacement of DMF with NMP as solvent did not give enhanced result (entry 19). As molecular iodine could be an effective catalyst or additive in some organic reactions,[18] iodine (20 mol %) was added into the catalytic system but did not improve the result (entry 20). Another experiment showed that $Cu(OTf)_2$, instead of $Cu(OAc)_2 \cdot H_2O$, gave lower result (entry 21).

Table 1
Screening conditions for copper-catalyzed N-arylation of morpholine[a]

Entry	Ligand	Cat.	Base	Additive	Yield[b] (%)
1	**E** (20%)	CuI (10%)	Cs_2CO_3	—	31
2[c]	**E** (20%)	CuI (10%)	Cs_2CO_3	—	Trace
3	**E** (20%)	CuI (10%)	K_2CO_3	—	2
4	**E** (20%)	CuI (10%)	K_3PO_4	—	Trace
5	**E** (20%)	CuI (10%)	KOH	—	2
6	**E** (20%)	CuI (10%)	KF	—	2
7	**E** (20%)	CuI (10%)	Pyridine	—	Trace
8	**E** (20%)	Cu powder (10%)	Cs_2CO_3	—	Trace
9	**E** (20%)	$Cu(OAc)_2 \cdot H_2O$ (10%)	Cs_2CO_3	—	39
10	**E** (20%)	$Cu(OAc)_2 \cdot H_2O$ (10%)	Cs_2CO_3	TBAC (10%)	31
11	**E** (20%)	$Cu(OAc)_2 \cdot H_2O$ (10%)	Cs_2CO_3	TBAB (10%)	27
12	**E** (20%)	$Cu(OAc)_2 \cdot H_2O$ (10%)	Cs_2CO_3	CTAB (10%)	31
13	**E** (30%)	$Cu(OAc)_2 \cdot H_2O$ (20%)	Cs_2CO_3	—	47
14	**E** (30%)	$Cu(OAc)_2 \cdot H_2O$ (10%)	Cs_2CO_3	—	Trace
15	**E** (20%)	$Cu(OAc)_2 \cdot H_2O$ (20%)	Cs_2CO_3	—	58
16	**E** (10%)	$Cu(OAc)_2 \cdot H_2O$ (10%)	Cs_2CO_3	—	12
17	**E** (30%)	$Cu(OAc)_2 \cdot H_2O$ (30%)	Cs_2CO_3	—	52
18	**E** (40%)	$Cu(OAc)_2 \cdot H_2O$ (40%)	Cs_2CO_3	—	46
19[d]	**E** (20%)	$Cu(OAc)_2 \cdot H_2O$ (20%)	Cs_2CO_3	—	34
20[e]	**E** (20%)	$Cu(OAc)_2 \cdot H_2O$ (20%)	Cs_2CO_3	—	37
21	**E** (20%)	$Cu(OTf)_2$ (20%)	Cs_2CO_3	—	16

[a] Reaction conditions: iodobenzene 1.0 mmol; morpholine 1.2 mmol; copper source 0.1 mmol; ligand 0.2 mmol; solvent—DMF 2 mL; base 3 mmol; temperature 140 °C; 20 h.

[b] Isolated yield.

[c] In air.

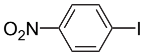
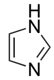
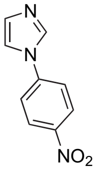
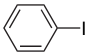
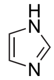
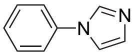
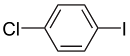
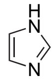
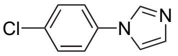
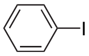
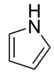
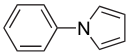
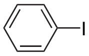
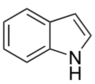
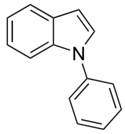
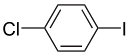
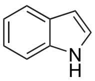
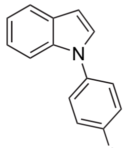
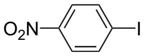
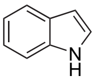
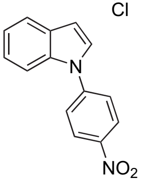
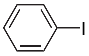
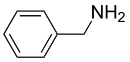
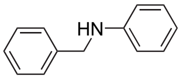
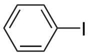
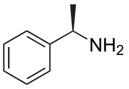
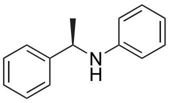
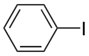
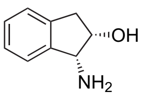
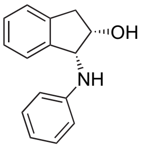
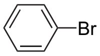
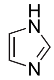
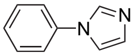
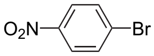
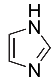
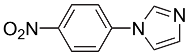
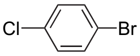
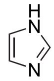
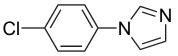
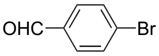
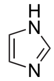
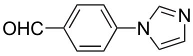
[d] The catalytic reaction was performed in NMP instead of DMF.

[e] I_2 (20 mol %) as additive.

Table 2
Coupling of aryl halide with various *N*-hetereocycles[a]

$$\text{Ar}-\text{X} \quad + \quad \text{Het-NH} \xrightarrow[\text{DMF, Cs}_2\text{CO}_3]{\substack{\text{20 mol\%Cu(OAc)}_2\cdot\text{H}_2\text{O} \\ \text{20 mol\% Hippuric acid}}} \text{Ar}-\text{N-Het}$$

X= I, Br, Cl   N-Heterocycle

Entry	ArX	Amine	Product	Time (h)	Yield (%)[b]
1				30	99
2				30	87
3				20	99
4				30	68
5				30	91
6				30	43
7				30	45
8				20	60
9				20	48
10				20	47
11				20	72
12				30	70
13				20	53
14				20	32

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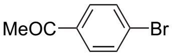
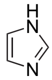
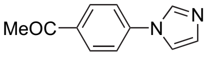
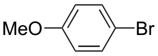
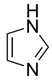
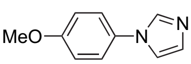
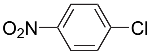
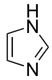
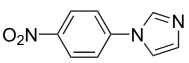
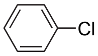
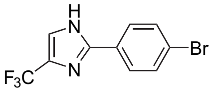
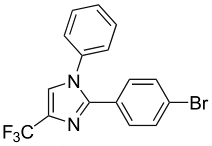
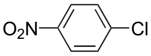
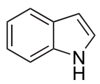
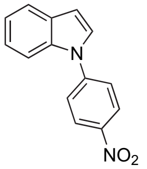
15				20	49
16				20	63
17				20	87
18				20	64
19				20	55

[a] Reaction conditions: iodobenzene 1.0 mmol; *N*-hetereocycle 1.2 mmol; $Cu(OAc)_2 \cdot H_2O$ 20 mol %; ligand 20 mol %; solvent—DMF 2 mL; Cs_2CO_3 3 mmol; temperature 140 °C; in argon atmosphere.

[b] Isolated yield.

As the development of an effective catalytic system for the coupling of imidazole is still far from being satisfactory, the optimized condition was employed in this reaction. The results are summarized in Table 2. We were delighted to find that the N-arylation of imidazole with a variety of aryl iodides proceeded smoothly to give the corresponding products in good to excellent yields (87–99%) (Table 2, entries 1–3). Subsequently, other similar *N*-hetereocycles, such as pyrrole and indole, were also tested as the substrates. The reactions also appeared to work well (entries 4–7). Furthermore, aliphatic amines including benzylamine, (*R*)-1-phenylethanamine, and (1*R*,2*S*)-*cis*-1-aminoindan-2-ol, were accessible using this protocol (entries 8–10). The isolated yields of the products varied from 43% to 60%. In addition, the coupling reactions of imidazole with aryl bromides or chlorides were carried out and the target products were obtained in moderate to good yields (entries 11–19). To our surprise, when the 4-nitrochlorobenzene was employed as arylating reagent, the yields appeared to be better than that of 4-nirobromobenzene.

In order to extend the application of our methodology, we attempted to apply the $Cu(OAc)_2 \cdot H_2O$/hippruric acid catalytic system to other coupling reactions, such as Sonogashira cross-coupling reaction. As shown in Scheme 1, under the non-optimized condition, the corresponding product was obtained in 43% yield. It was encouraging to reveal that our catalytic system could be efficient in other coupling reactions. The further work is underway in our laboratory.

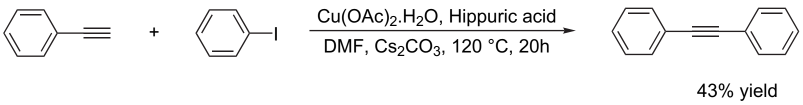
3. Conclusion

In summary, an inexpensive and efficient $Cu(OAc)_2 \cdot H_2O$/hippruric acid system has been developed for the C–N coupling reactions of imidazoles or other heterocycles with aryl iodides, bromides, or chlorides, providing the corresponding products with moderate to excellent yields. In comparison to other transition-metal catalyst systems, such as palladium-catalyzed arylamination, this protocol is simple and avoids the use of air-sensitive and expensive catalysts or additives. Further work is in progress in this laboratory to apply this catalytic system to other processes and to study the mechanism of this copper-catalyzed C–N coupling reaction.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere condition. Solvents were dried and degassed by standard methods and all nitrogen-containing heterocycles and aryl halides were purchased from Aldrich and Alfa. Flash column chromatography was performed using silica gel (300–400



Scheme 1. Sonogashira cross-coupling reaction catalyzed by $Cu(OAc)_2 \cdot H_2O$/hippruric acid system.

mesh). Analytical thin layer chromatography was performed using glass plates pre-coated with 200–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). NMR spectra were measured in $CDCl_3$ on a Varian Inova-400 NMR spectrometer (400 or 300 MHz) with TMS as an internal reference. Products were characterized by comparison of ^1H and ^{13}C NMR data with that in the literatures.

4.2. General procedure for C–N coupling reactions of aryl halide and heterocycle

$Cu(OAc)_2 \cdot H_2O$ (0.2 equiv), cesium carbonate (3.0 equiv), and hippuric acid (0.2 equiv) were added to a screw-capped test tube. The tube was then evacuated and backfilled with argon (three cycles). DMF (2 ml), heterocycles (1.2 equiv) (if liquid), and aryl halide (if liquid) were added by syringe at room temperature. The tube was again evacuated and backfilled with argon (three cycles). The mixture was heated to 120–140 °C and stirred for 20–30 h. After cooling to room temperature, the mixture was diluted with water, and the combined aqueous phases were extracted three times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, and concentrated to yield the crude product, which was further purified by silica gel chromatography, using petroleum ether and ethyl acetate as eluents to provide the desired product.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.11.054.

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