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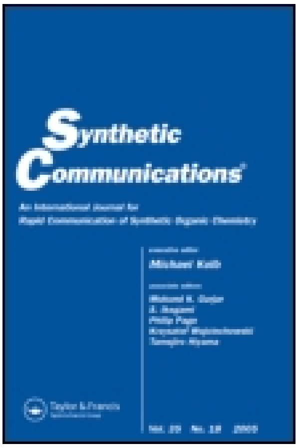

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Efficient and Reusable Catalytic System of CuI-PEG for N-Arylation of Imidazoles

Qiang Zhang [a] , Jun Luo [a] & Yunyang Wei [a]

[a] School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing, China

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EFFICIENT AND REUSABLE CATALYTIC SYSTEM OF CuI-PEG FOR *N*-ARYLATION OF IMIDAZOLES

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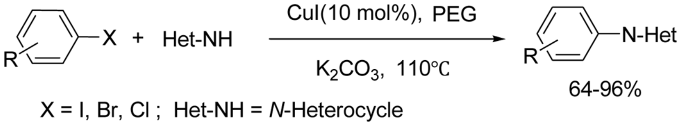
School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing, China

GRAPHICAL ABSTRACT



Abstract *A simple, efficient, and recyclable catalytic system of CuI–poly(ethylene glycol) (PEG) was developed for the* N-*arylation of imidazoles with aryl halides to afford corresponding* N-*arylimidazoles in good to excellent yields under mild conditions and free of any additional ligands and solvents. The isolation of the products was readily performed by simple extraction with ether, and the catalytic system could be reused without remarkable loss of activity even after six runs.*

Keywords Copper; *N*-arylimidazoles; PEG; Ullmann-type coupling

INTRODUCTION

Nitrogen-containing heterocycles such as *N*-arylimidazoles play an important role in a wide range of pharmaceuticals,[1] biologicals,[2] natural products,[3] and *N*-heterocyclic carbene chemistry.[4] Traditionally, these *N*-arylimidazoles have been prepared by nucleophilic substitution of imidazoles with electron-deficient aryl halides or the classical Ullmann-type coupling.[5] However, these well-known methods generally suffer from several drawbacks, such as reaction temperature as high as 200 °C, use of stoichiometric amounts of copper reagents, moderate yields, and poor substrate scope. In some instances, palladium catalysts assisted by some phosphine ligands have been employed to make the reaction take place under mild conditions.[6] Recently, Buchwald *et al.*[7] and Taillefer *et al.*[8] have discovered and developed copper catalytic paths for the *N*-arylation of nitrogen-containing hererocycles with aryl halides in the presence of *N*- and *O*-based ligands under relatively mild conditions. From then on, a number of copper-catalyzed coupling reactions with various ligands have been reported.[9] Nevertheless, these methods are generally

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Address correspondence to Jun Luo, School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China. E-mail: luojun@mail.njust.edu.cn

performed in volatile organic solvents and in nonrecyclable catalytic systems. Hence, the development of simple and green methods for the C-N coupling reaction is of particular value.

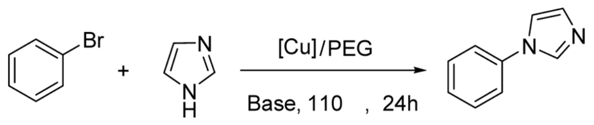
Poly(ethylene glycol) (PEG) has been successfully used as a reaction medium for metal-catalyzed reactions with easy recycling of solvents and catalysts.[10] In addition, because PEG is inexpensive, readily available, easily degradable, and less toxic, many studies have also covered PEG chemistry.[11] Herein, we report a simple and efficient *N*-arylation of imidazoles with aryl halides in a recyclable catalytic system of CuI-PEG.

RESULTS AND DISCUSSION

The *N*-arylation of imidazole and bromobenzene was selected as the model reaction to optimize the reaction conditions, and the results are shown in Table 1. Some readily available copper sources were investigated, and it was found that CuI sources were more favored (entries 1–5), which is in agreement with the previous reports.[9a,9b,12] As CuI turned out to give the best result, it was chosen as the standard Cu source for the following experiments. Subsequently, various bases were screened. Cs_2CO_3, K_2CO_3, $K_3PO_4 \cdot 3H_2O$, and KOH were found to be highly effective (entries 2, 8–10). Other inorganic bases such as KF, Na_2CO_3, and NaOAc led to moderate yields (entries 11–13), while NEt_3 and dimethylaminopyridine (DMAP) proved to be inefficient bases (entries 14 and 15). Therefore, the cheap and mild base K_2CO_3 was chosen as the standard base. Moreover, all the PEGs tested afford similar results (entries 2 and 18–20). Because PEG_{200} had less viscosity, it was chosen as the medium. The control experiments showed that the presence of catalyst, base, and PEG was crucial for the reaction. No product was detected in the absence of copper salt, while only 31% yield was obtained in the absence of base (entries 6 and 7), and 52% yield was obtained in the absence of PEG (entry 16). In addition, the catalytic reactions performed in air afforded the product with 82% yield (entry 22), and at lower temperature (90 °C) only moderate yield was obtained (entry 23).

With the optimal conditions in hand, different aryl halides were used for *N*-arylation of imidazole in the presence of 10 mol% CuI and 2 equiv of K_2CO_3 in PEG_{200} at 110 °C under N_2, and the results are listed in Table 2. The results indicated clearly that this method was applicable for *N*-arylation of imidazole with a variety of aryl bromides, and the yields were also good (64–96%) (entries 1–10). In general, substrates possessing electron-withdrawing groups (such as *p*-NO_2, *p*-CF_3, and *m*-CF_3 groups) proceeded quickly to give excellent yields (entries 1–3). Bromoarenes bearing electron-donating groups (such as *p*-CH_3, *p*-OH, *p*-OMe, and *o*-OMe) afforded coupling products with moderate to excellent yields ranging from 64% to 90% with longer reaction time (up to 48 h) (entries 5–8). It is noteworthy that the reaction was highly chemoselective; for example, the coupling reaction between 1-bromo-4-chlorobenzene and imidazole gave *N*-(4-chlorophenyl) imidazole as the sole product (Table 2, entry 9). In particular, imidazole could be selectively arylated by 4-bromophenol in satisfactory yields without formation of diaryl ether (entry 8). As usual, free hydroxyl should be protected before *N*-arylation.[13] Attempts to use chlorobenzene as aryl source failed; however, the employment of several aryl chloride possessing electron-withdrawing groups (such as *p*-NO_2, *o*-NO_2, and *p*-CF_3 groups) led to the

Table 1. *N*-Arylation of imidazole with bromobenzene under different reaction conditions[a]



Entry	Cu cat.	Base	PEG	Yield (%)[b]
1	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	PEG_{200}	89
2	CuI	K_2CO_3	PEG_{200}	97
3	CuBr	K_2CO_3	PEG_{200}	93
4	CuCl	K_2CO_3	PEG_{200}	87
5	Cu	K_2CO_3	PEG_{200}	85
6	—	K_2CO_3	PEG_{200}	0
7	CuI	—	PEG_{200}	31
8	CuI	Cs_2CO_3	PEG_{200}	98
9	CuI	$K_3PO_4 \cdot 3H_2O$	PEG_{200}	95
10	CuI	KOH	PEG_{200}	97
11	CuI	KF	PEG_{200}	82
12	CuI	Na_2CO_3	PEG_{200}	65
13	CuI	NaOAc	PEG_{200}	70
14	CuI	NEt_3	PEG_{200}	28
15	CuI	DMAP	PEG_{200}	24
16	CuI	K_2CO_3	—	52[c]
17	CuI	K_2CO_3	—	95[d]
18	CuI	K_2CO_3	PEG_{600}	97
19	CuI	K_2CO_3	PEG_{1000}	96
20	CuI	K_2CO_3	PEG_{2000}	95
21	CuI	K_2CO_3	PEG_{200}	85[e]
22	CuI	K_2CO_3	PEG_{200}	82[f]
23	CuI	K_2CO_3	PEG_{200}	61[g]

[a] Reaction conditions: bromobenzene (2.0 mmol), imidazole (2.4 mmol), and base (4.2 mmol) in the presence of 10 mol% of Cu catalyst in 3 mL of PEG at 110 °C for 24 h under N_2.

[b] Determined by GC-MS.

[c] Pure DMSO (3 mL) was used instead of PEG.

[d] 10 mol% PEG_{200}-DMSO (3 mL) was used.

[e] The amount of catalyst is 5 mol%.

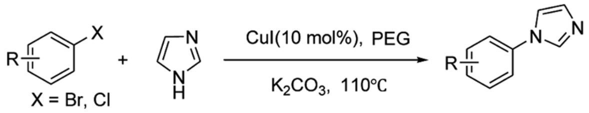
[f] The catalytic reaction was performed in air.

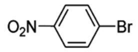
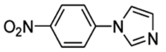
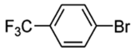
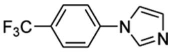
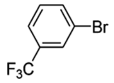
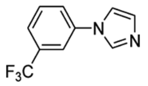
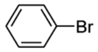
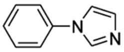
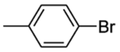
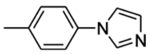
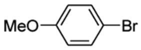
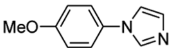
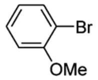
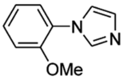
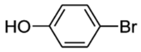
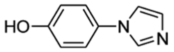
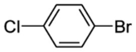
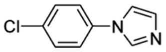
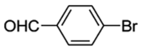
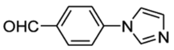
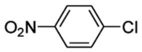
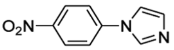
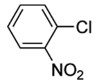
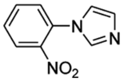
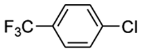
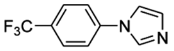
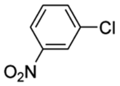
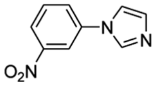
[g] The catalytic reaction was performed at 90 °C.

corresponding coupling product in good to excellent yields (70–95%) (entries 11–13). Actually, only a few articles have described copper-catalyzed *N*-arylation of imidaolze with aryl chlorides.[14]

In an endeavor to expand the scope of the methodology, other π-electron-rich nitrogen heterocycles such as benzimidazole, 2-methylimidazole, indole, and pyrrole were coupled with aryl halides to give the corresponding *N*-arylated products in good to excellent yields (Table 3). For example, the coupling reaction of 1*H*-benzimidazole with bromobenzene afforded the corresponding product in 73% yield (entry 2). The sterically hindered 2-methylimidazole could also undergo efficient *N*-arylation with 4-nitrochlorobenzene and 4-bromobenzotrifluoride to give the corresponding products in good yields (entries 4 and 5). Moreover, the *N*-arylation of indole and pyrrole

Table 2. *N*-Arylation of imidazole with different aryl halides catalyzed by CuI-PEG system[a]



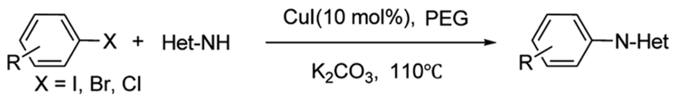
Entry	Aryl halide	Product	Time (h)	Yield (%)[b]
1			18	96
2			18	95
3			18	91
4			24	93
5			24	90
6			24	80
7			48	64[c]
8			24	82
9			24	86
10			36	85
11			24	95
12			24	88
13			36	70
14			48	35

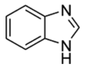
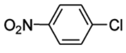
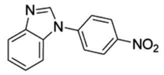
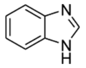
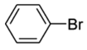
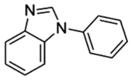
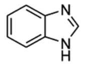
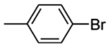
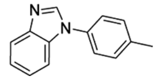
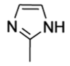
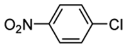
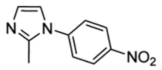
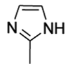
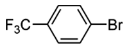
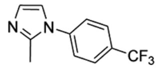
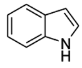
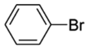
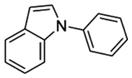
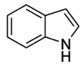
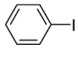
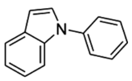
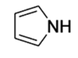
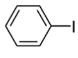
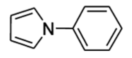
[a] General reaction conditions: aryl halide (2.0 mmol), imidazole (2.4 mmol), and K_2CO_3 (4.2 mmol) in the presence of 10 mol% of CuI in 3 mL of PEG_{200} at 110 °C under N_2.

[b] Isolated yield.

[c] 20 mol% of CuI.

Table 3. *N*-Arylation of imidazoles with aryl halides catalyzed by CuI-PEG system[a]



Entry	Het-NH	ArX	Product	Yield (%)[b]
1				90
2				73[c]
3				82[c]
4				81
5				72
6				63
7				94
8				91

[a] General reaction conditions: aryl halide (2.0 mmol), N-heterocycle (2.4 mmol), K_2CO_3 (4.2 mmol) in the presence of 10 mol % of CuI in 3 mL of PEG_{200} at 110 °C for 24 h under N_2.

[b] Isolated yield.

[c] 36 h at 110 °C.

with iodobenzene could also be conducted smoothly to give excellent yields in 94% and 91%, respectively (entries 7 and 8).

The recyclability experiment was performed on the coupling of imidazole and bromobenzene in the CuI-PEG_{200} system. Notably, isolation of the product and catalytic system was very simple and convenient. When the final reaction mixture was cooled to room temperature, diethyl ether was added, and the upper layer of ether containing product was separated by decantion. The lower layer containing PEG and Cu catalyst was subjected to a second run of the *N*-arylation by charging it with fresh imidazole, bromobenzene, and potassium carbonate. The procedure was repeated six times, and the results indicated that the CuI-PEG_{200} system could be recycled without apparent loss of catalytic activity (Fig. 1).

In summary, we have developed a simple, highly efficient, and environmentally friendly method for the *N*-arylation of imidazoles with aryl halides catalyzed by CuI in PEG without any additional ligand. Particularly noteworthy are the facts that this method avoids the use of volatile organic solvents and that the catalytic system can

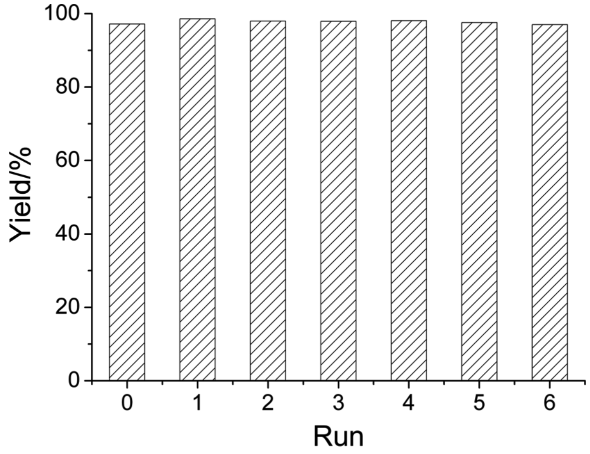


Figure 1. Recycling experiment of the CuI-PEG$_{200}$ system.

be easily recycled. In addition, this method can be performed simply and tolerates a variety of functional groups, such as aldehyde, nitro, ether, and free hydroxyl. Thus, we believe that this method may provide wide application in preparation of *N*-arylated products.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker DRX300 (300 MHz). Mass spectra were obtained with automated Fininigan Trace Ultra-Trace DSQ gas chromatography–mass spectrometry (GC/MS) spectrometer. All chemicals (analytical reagent) were commercially available and used without further purification.

General Procedure for the Coupling Reaction

A Schlenk tube with a magnetic stirring bar was charged with imidazole (2.4 mmol), K_2CO_3 (4.2 mmol), CuI (0.16 mmol, 10 mol%), aryl halide (2.0 mmol), and PEG (3 mL). The tube was sealed after being evacuated twice and back filled with N_2. The mixture was stirred at 110 °C for 24 h, cooled to room temperature, and extracted with diethyl ether (5 × 10 mL). The upper layers were decanted, combined, and concentrated to the crude product, which was analyzed by GC-MS. The PEG phase of the lower layer was subjected to a second run with the same substrates. Further purification of the product was achieved by flash chromatography on a silica-gel column. All the products, which are known compounds, were characterized and compared with authentic compounds previously reported in the literatures.[9a,9b,12,15] Some typical data of products was provided as follows.

Selected Data

1-(4-Trifluoromethylphenyl)-1*H*-imidazole (Table 2, Entry 2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.76 (d, 2H, $J = 9.0$ Hz), 7.54 (d, 2H, $J = 9.0$ Hz), 7.34 (s, 1H), 7.25 (s, 1H). GC-MS (EI, m/z): 211.9 [M$^+$].

1-(3-Trifluoromethylphenyl)-1*H*-imidazole (Table 2, Entry 3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.67–7.61 (m, 4H), 7.34 (s, 1H), 7.26 (s, 1H). GC-MS (EI, *m*/*z*): 211.9 [M^+].

1-Phenyl-1*H*-imidazole (Table 2, Entry 4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.50–7.45 (m, 2H), 7.40–7.34 (m, 3H), 7.27 (s, 1H), 7.20 (s, 1H). GC-MS (EI, *m*/*z*): 144.0 [M^+].

1-(4-Methoxyphenyl)-1*H*-imidazole (Table 2, Entry 6). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.34–7.31 (m, 2H), 7.22 (s, 1H), 7.20 (s, 1H), 7.02–6.99 (m, 2H), 3.87 (s, 3H). GC-MS (EI, *m*/*z*): 173.9 [M^+].

1-(4-Nitrophenyl)-1*H*-imidazole (Table 2, Entry 11). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, 2H, $J = 9.0$ Hz), 8.01 (s, 1H), 7.60 (d, 2H, $J = 9.0$ Hz), 7.41 (s, 1H), 7.31 (s, 1H). GC-MS (EI, *m*/*z*): 188.9 [M^+].

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