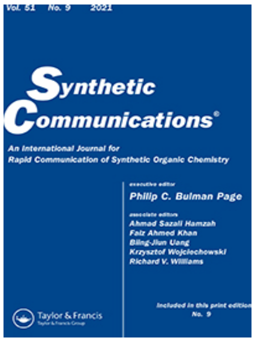

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A ligand-free copper-catalyzed strategy to the N-arylation of indazole using aryl bromides

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ABSTRACT
A simple and efficient strategy for the C–N cross-coupling of indazole with a variety of substituted aryl bromides is reported. Under the optimized conditions, a broad scope of N-arylated products were obtained in good to excellent yields (up to 87%) under the ligand-free conditions.

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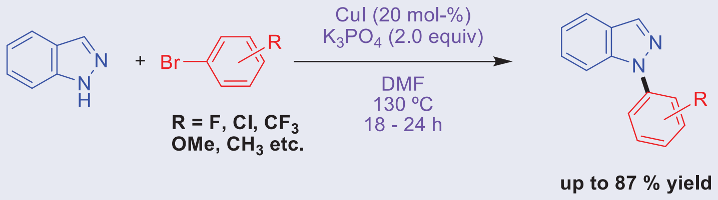
KEYWORDS
Indazole; copper (I) iodide; aryl bromides; ligand-free; N-arylation

GRAPHICAL ABSTRACT



Introduction

Nitrogen-containing heterocycles serve as an important class of synthesized compounds found in various natural products and biologically active pharmaceuticals.[1] In particular, N-arylindazole exhibits useful biological responses as anti-inflammatories and anticancer compound.[2]

Ullmann-type coupling has attracted great interest among the synthetic community as it offers numerous application options such as N-, O-, C-aryl bond formations.[3] Moreover, copper catalysis offers more advantages due to its lower cost[4] and ability to work well for the arylation of several nucleophiles.[5] However, this classical copper-catalyzed coupling has its limitations, for example, high reaction temperature, highly polar solvents and high catalyst loadings.[6] In this context, some of the limitations can be overcome by the use of suitable mono- or bidentate ligands such as diamines,[7] 1,10-phenanthroline,[8] amino acids,[9] and nitrogen containing ligands[10] to enhance the reactivity of the copper catalysts, broaden the substrate scope and also to achieve a milder reaction condition. However, the use of ligands has its disadvantages such as additional cost, and a need for special synthesis under inert conditions in some instances.

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Henceforth, the development of ligand free catalytic system for N-arylation of azoles is of great significance since it offers a more cost effective and strategy. Correa and Bolm reported the N-arylation of sulfoximines and nitrogen heterocycles with aryl halides using a ligand free Cu_2O catalytic system.[11]

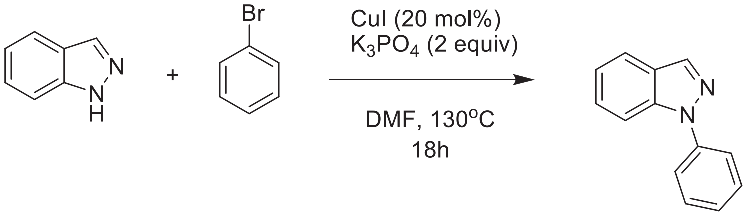
Xu reported a reusable catalytic system for N-arylation of a variety of nitrogen-containing heterocycles with aryl and heteroaryl halides using Cu_2O.[12] However, the substrate scope for aryl bromides is limited to imidazole in the presence of a strong KOH base. Rossi demonstrated a CuOAc-mediated C–N coupling reactions of indoles and carbazole with aryl iodides under ligand-free and base-free conditions.[13] Chan developed a successful protocol for the coupling of nitrogen heterocycles with aryl iodides under ligand-free conditions using Cu(I) halide salts with NaOH as base and Bu_4NBr as the phase transfer catalyst.[14] Sperotto also reported an efficient protocol for the coupling of various nitrogen nucleophiles with aryl halides under copper-catalyzed ligand-free condition.[15] Similarly, the protocol reported efficient coupling of imidazole with limited aryl bromides scope as the electrophilic reagents at 160 °C.

The majority of these ligand-free catalytic systems developed utilize mostly aryl iodides as the electrophilic coupling partners to ensure efficiency of the catalytic systems. The use of aryl bromides remained limited due to the lower reactivities of such reagents under the ligand-free reaction conditions. However, aryl bromides offer added advantages compared to the iodide counterparts due to its lower toxicity and costs. To the best of our knowledge, cross coupling reaction of indazoles with substituted aryl bromides under ligand-free conditions has not been reported. Henceforth, as part of our efforts to develop more practical and cost effective cross-coupling technologies, we envisaged the application of the ligand-free systems established in our research group[16] for the N-arylation of indazoles using aryl bromides as the electrophilic partners.

Results and discussion

In our initial study, indazole and bromobenzene were chosen as model substrates for the copper-catalyzed N-arylation reaction. Under the ligand-free conditions with CuI as the catalyst, the reaction gave a favorable yield of 66% of the product (Table 1, entry 1). In order to optimize the reaction, the efficiency of various copper sources for the arylation reaction was investigated (entries 1–5). Among them, CuBr and CuCl gave modest yields, (entries 2 and 3) affording the products in 64% and 61%, respectively. However, the use of Cu_2O was not efficient which gave the product in a poor yield of 19% (entry 4), while Cu as catalyst afforded the product in a moderate yield of 42% (entry 5). Next, the solvent effect of commonly used organic solvents as reaction medium was explored. In this study, DMF proved to be the best solvent that gave rise to a yield of 66%. However, the findings also demonstrated that DMSO is another suitable solvent, giving a yield of 65% (Table 1, entry 7). Further experiments revealed that K_3PO_4 is the ideal choice as the base for the coupling reaction as Na_2CO_3, K_2CO_3 and Cs_2CO_3 resulted in lower yields (entries 10–12). A scale up reaction using 1 g of indazole with 3 equiv of bromobenzene under the optimized condition was attempted which gave the N-arylated product in a good yield of 71%.

Table 1. Optimization studies of ligand-free copper-catalyzed cross coupling of indazole and bromobenzene[a].



Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	CuI	K_3PO_4	DMF	66
2	CuBr	K_3PO_4	DMF	64
3	CuCl	K_3PO_4	DMF	61
4	Cu_2O	K_3PO_4	DMF	19
5	Cu	K_3PO_4	DMF	42
6	CuI	K_3PO_4	t-Butanol	55
7	CuI	K_3PO_4	DMSO	65
8	CuI	K_3PO_4	Dioxane	48
9	CuI	K_3PO_4	Toluene	39
10	CuI	Na_2CO_3	DMF	Trace
11	CuI	K_2CO_3	DMF	56
12	CuI	Cs_2CO_3	DMF	63

[a] Unless otherwise shown, the reaction was carried out with indazole (1.5 mmol), bromobenzene (2.25 mmol), K_3PO_4 (3.0 mmol), Cu source (20 mol%) in DMF (0.75 ml) at 130 °C for 18 h.
[b] Isolated yield after column chromatography.

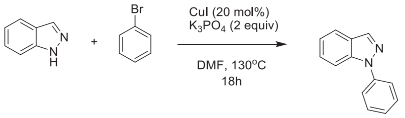
In summary, the optimized conditions for our ligand-free copper-catalyzed cross-coupling reaction was achieved using a combination of CuI (20 mol%), K_3PO_4 (2 equiv) in DMF at 130 °C for 18 hours.

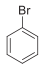
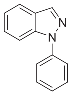
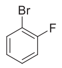
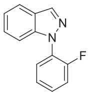
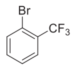
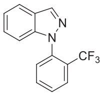
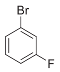
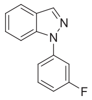
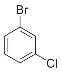
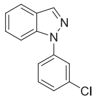
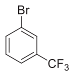
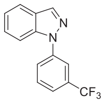
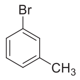
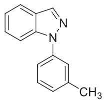
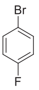
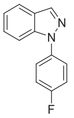
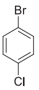
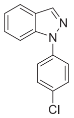
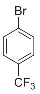
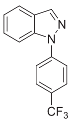
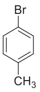
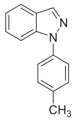
To examine the generality of this protocol, a variety of *ortho*-, *meta*-, and *para*-substituted bromobenzenes were coupled with indazole under the optimized condition. In general, good to excellent yields were obtained for cross-coupling of sterically unhindered bromobenzenes.

The findings concur that *ortho*-substituted bromobenzene was not suitable electrophilic partners due to steric hindrance effect except for 2-F and 2-CF_3 substituted bromobenzene (Table 2, entries 2 and 3). No significant electronic effects were observed for both meta- and para-substituted bromobenzene (entries 4–11) except for OMe substituent which gave trace amount of products. However, reactions attempted using 2-, 3- and 4-bromopyridines as electrophilic partners were not successful as these substrates gave only trace amount of the products.

In order to expand the scope of this ligand-free CuI catalytic system, the cross-coupling reactions between a series of nitrogen heterocycles and bromobenzene were carried out. (Table 3, entries 1–5). Notably, pyrazole gave the best yield of 95% under the cross coupling reaction with bromobenzene (entry 1). Moderate yields were obtained in the case of 7-azaindazole and indole (entries 4 and 5) as coupling partners. However, the reaction using pyrrole was not encouraging as only trace amount of the product was obtained. Next, we broaden the scope of the nucleophilic partners to include representative sulfonamides and amides. In this case, sulfonamides proved to be efficient reagents under the reaction conditions, affording the corresponding N-arylated

Table 2. CuI-catalyzed N-arylation of indazole with substituted aryl bromides.[a].



Entry	ArX	Product		Yield [b] (%)
1			**3a**	66
2			**3b**	57
3			**3c**	37
4			**3d**	75
5			**3e**	69
6			**3f**	78
7			**3g**	68
8			**3h**	73
9			**3i**	79
10			**3j**	87
11			**3k**	60%

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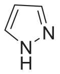
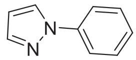
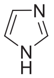
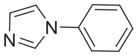
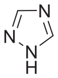
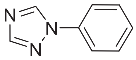
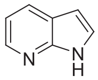
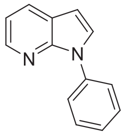
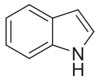
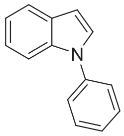
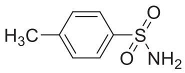
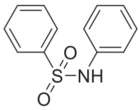
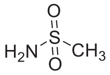
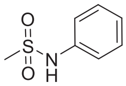
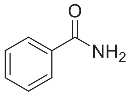
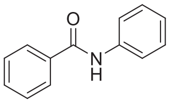
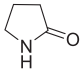
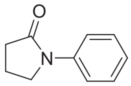
[a] Unless otherwise shown, the reaction was carried out with indazole (1.5 mmol), bromobenzene (4.5 mmol), K_3PO_4 (3.0 mmol), CuI (20 mol%) in DMF (0.75 ml) at 130 °C for 18 h.

[b] Isolated yield after column chromatography.

Table 3. CuI-catalyzed N-arylation of substituted N-containing nucleophiles with bromobenzene.[b].

Entry	Amine	Product		Yield[b] (%)
1			**4a**	95
2			**4b**	56
3			**4c**	71
4			**4d**	40
5			**4e**	43
6			**4f**	62
7			**4g**	75
8			**4h**	49
9			**4i**	32

[a]Unless otherwise shown, the reaction was carried out with substituted N-heterocycle (1.5 mmol), bromobenzene (4.5 mmol), K_3PO_4 (3.0 mmol), CuI (20 mol%) in DMF (0.75 ml) at 130 °C for 18 h.
[b]Isolated yield after column chromatography.

products in good yields (entries 6 and 7). However, the use of benzamide and pyrrolidinone gave the products in lower yields of 49% and 32%, respectively.

Experimental

General procedure for N-arylation of indazole

A mixture of CuI (Sigma-Aldrich, 99.99% purity, 0.3 mmol), K_3PO_4 (3.0 mmol) and indazole (1.5 mmol) was dissolved in (0.75 ml) dimethylformamide (DMF). Following, the bromobenzene (2.25 mmol) was added to the reaction vial. The reaction vial was then sealed tightly with a screw cap and the reaction was allowed to stir at room temperature for 5 minutes. The reaction mixture was stirred under air in a closed system at 130 °C for 18 h in an oil bath, following the reaction mixture was then cooled to room temperature with dichloromethane (DCM). The resulting solution was directly filtered through a pad of Celite and washed with dichloromethane for a few times. The combined organic extracts were dried with anhydrous Na_2SO_4 and removed by filtration. Subsequently, the crude product was purified by silica-gel column chromatography to afford the N-arylated product. The purity, identity and structure of the final product was confirmed by ^{1}H, ^{13}C NMR spectroscopic analysis and elemental analysis.

1-Phenyl-1-indazole (3a)

223.5 mg (77%) of the coupled product was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ8.21 (s, 1H), δ7.81(d, $J = 6.8$ Hz, 1H), δ7.74–7.78 (*m*, 3H), δ7.55 (*t*, $J = 7.8$ Hz, 2H), δ7.44 (*t*, $J = 7.6$ Hz, 1H), δ7.37 (*t*, $J = 7.2$ Hz, 1H), δ7.22–7.26 (*m*, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): 140.2, 138.7, 135.4, 129.4, 127.1, 126.6, 125.3, 122.7, 121.5, 121.3, 110.4

Anal. Calculated for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 79.96 H, 5.17; N, 14.19

All spectral data correspond to those given in the literature.[16(b)]

Conclusion

In summary, we have developed a simple, versatile and viable ligand-free CuI-catalyzed cross coupling protocol for the arylation of various nitrogen heterocycles with different substituted aryl bromides. In most instances, this protocol generates the N-heterocyclic products in moderate to good yields. The economical and simple reaction conditions offer ease of transfer to industrial scale operations.

Supporting Information: Full experimental detail, ^{1}H and ^{13}C NMR spectra and elemental analysis. This material can be found via the "Supplementary Content" section of this article's webpage.'

Funding

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