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Graphical Abstract

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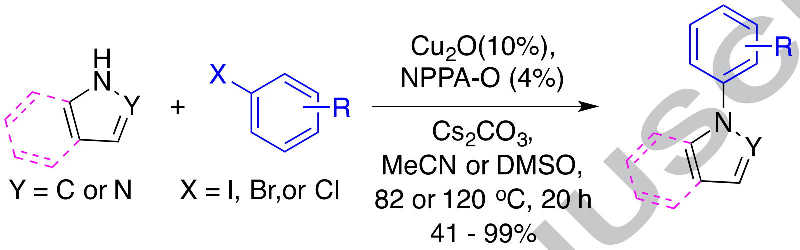

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N-Picolinamides as ligands for Ullmann-type C-N coupling reactions

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ABSTRACT

The use of *N*-phenyl-2-pyridincarboxamide-1-oxide as a ligand with Cu_2O in Ullmann type C-N bond formations between aryl halides and *N*-heteroaryls in common solvents, such as MeCN, DMF, and DMSO at 82-120 °C has been successfully demonstrated. The ligand is effective when only 4% equiv is used relative to the substrate. The reaction provided the corresponding products in coupling of electron-rich, electron poor, and ortho-substituted aryl halides, including ortho aryl-chlorides, in good to very good yields. *N*-Arylation is selectively preferred at the benzyl position when ortho-halide benzyl bromide is reacted with one equivalent of pyrazole. However, di-*N*-arylation is achieved in very high yields when 2.5 equiv of pyrazole is used, providing a stoichiometric control over the coupling reaction.

Since its discovery by Fritz Ullmann and Irma Goldberg in the early 1900s,[1] the Ullmann reaction has become one of the general methods for C–C, C–N, and C–O bond formations in aryl couplings.[2] It has been applied in the synthesis of natural products, compounds with medicinal importance, agrochemicals, and materials with unique electronic and structural properties.[3] However, the Ullmann reaction has not been the preferred method until recently, because of its main drawbacks: the necessity of high temperatures and need of high boiling polar solvents. On the other hand, C-N cross couplings utilizing palladium catalysts, developed by Buchwald-Hartwig, also have limitations, which are mainly high reaction temperatures, long reaction time, and high cost of palladium catalysts and their severe toxicity.[4]

Development of ligands for Ullmann type copper catalyzed coupling reactions by Buchwald,[5] Nicolaou,[6] Liebeskind,[7] and Ma[8] resulted in improved reaction conditions with wider substrate scope. Therefore, extensive research efforts have been devoted to promote alternative ligands to overcome of the limitations of copper catalyzed reactions in Ullmann type couplings in order to reduce the catalyst loadings and increase the yields using moderate reaction conditions.[2, 9] The use of ligands with copper salts in catalytic amounts have been shown to be highly economical and versatile method compared to palladium catalyzed systems. They are less expensive, environmentally friendly, and easy to purify and scale up.

Several class of ligands have been developed for Ullmann type C-N bond formations, including phenanthrolines,[10] amino alcohols,[11] diamines,F[12] diols,F[13] β-diketones and β-keto esters,[14] and others.[9] Recently, various pyridine *N*-oxides have been also successfully employed as ligands in copper catalyzed C-N coupling reactions.[15] Picolinamide derived ligands have also been successfully employed as ligands in group-directed C-H bond activation[16] and in asymmetric Mannich-type reactions.[17]

In our previous study, we successfully demonstrated the first use of *N*-phenylpicolinamide (NPPA, **L4**) as an efficient ligand to form aryl-aryl C-C bonds in Ullmann type homocoupling, including aryl chlorides, and in base-free Suzuki-type heteroaryl coupling.[18] In continuation of our research on ligand development for Ullmann-type copper catalyzed couplings, we herein successfully demonstrate the use of *N*-phenylpicolinamide-1-oxide (NPPA-N-Oxide) as a ligand for Ullmann-type C-N coupling reactions of aryl iodide, aryl bromide as well as aryl chloride with various *N*-arylheterocycles in acetonitrile or DMSO at moderate temperatures.

For our preliminary studies, the coupling reaction of pyrazole and 4-bromonitrobenzene was investigated to optimize reaction conditions including ligand, solvent, base, and the copper source by following our general coupling procedure (Table 1).[19]

First, to explore the role of ligands on catalytic activity, several ligands **L1-L5** were screened for *N*-arylation of pyrazole with 4-Bromonitrobenzene using 10 mol % of activated copper and Cs_2CO_3 in acetonitrile (MeCN) at reflux temperature (Table 1, entries 1-5). When picolinic acid (**L1**) and picolinic acid *N*-oxide (**L2**) were used as the ligands, the coupled product was obtained in only 41% and 52% yields, respectively (Table 1, entries 1 and 2), which were similar to the literature results.[14a,b] When picolinamides **L3 and L4** were used as ligands, the reaction provided yields in 70 and 77%, respectively (Table 1,

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entries 3 and 4). However, *N*-oxide on the pyridine moiety of picolinamide **L5** (NPPA-O) significantly increases the reactivity of the ligand by providing the coupled product in 92% yield in MeCN at 82 ^{o}C (Table 1, entry 5).

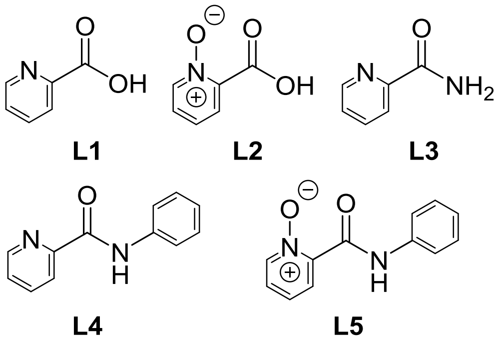
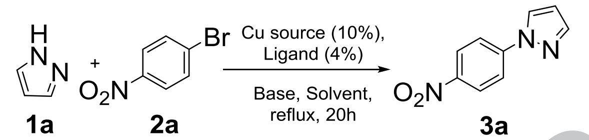


Figure 1. Structures of ligands which were surveyed in Table 1.

The comparison of ligands **L2**, **L4**, and **L5** shows the importance of the both phenyl amide and *N*-pyridyl oxide moieties for increased activity. The importance of the *N*-phenyl amide moiety, which may have both electronic and steric effects on ligand activity, was also shown in our previous study in homocoupled C-C bond formations.[18] On the other hand, the reaction provided almost no product without any ligand, showing its necessity for activity (Table 1, entry 6).

Table 1. Survey of ligand, base, copper source, and solvent.



Entry	Ligand	Base	Copper source	Solvent	Yield (%)[a]
1	L1	Cs_2CO_3	Cu	MeCN	41
2	L2	Cs_2CO_3	Cu	MeCN	52
3	L3	Cs_2CO_3	Cu	MeCN	70
4	L4	Cs_2CO_3	Cu	MeCN	77
5	L5	Cs_2CO_3	Cu	MeCN	92
6	-	Cs_2CO_3	Cu	MeCN	3
7	L5	Cs_2CO_3	Cu	Dioxane	NR
8	L5	Cs_2CO_3	Cu	THF	5
9	L5	Cs_2CO_3	Cu	DMF	91
10	L5	Cs_2CO_3	Cu	DMSO	91
11	L5	K_2CO_3	Cu	MeCN	NR
12	L5	K_3PO_4	Cu	MeCN	NR
13	L5	Cs_2CO_3	CuI	MeCN	52
14	L5	Cs_2CO_3	CuBr	MeCN	74
15	L5	Cs_2CO_3	$CuBr_2$	MeCN	77
16	L5	Cs_2CO_3	Cu_2O	MeCN	95
17	L5	Cs_2CO_3	-	MeCN	9[b]

[a] Isolated yield. [b] The reaction was carried out at 120 ^{o}C

It has been shown that the coordination properties of *N*-oxide and the carboxyl group of picolinic acid *N*-oxide or its substituted derivatives would be capable of participating in the formation of six-membered-ring coordinates with a copper center.[15a]

N-arylation of pyrazole in the presence of NPPA-O in both DMF and DMSO gave similar results (91%) to MeCN (Table 1, entries 9 and 10), while the reaction in dioxane or THF provided either no or very low yield, respectively (Table 1, entries 7 and 8). The results with NPPA-O as a ligand allowed the use of three common solvents (MeCN, DMF and DMSO) for the Ullmann-type C-N bond formations at 82 ^{o}C.

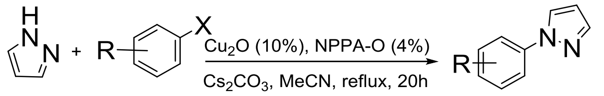
When K_2CO_3 or K_3PO_4 was used as a base, the starting materials were recovered completely, which made Cs_2CO_3 as the base choice for the C-N bond formations (Table 1, entries 5, 11-12). Finally, in addition to activated copper, several other copper sources such as activate copper CuI, CuBr, $CuBr_2$ and Cu_2O were also evaluated by using NPPA-O as ligand. The reactions with CuI, CuBr, $CuBr_2$ produced the coupled products in modest to good yields (52-77%, Table 1, entries 13, 14 and 15), but lower than the reaction which is used activated copper (92%). To our delight, Cu_2O was selected as the best copper salt to promote the highest yield of C-N coupling (95%, Table 1, entry 16), even better than activate copper. In the absence of any copper metal source in the reaction, only a 9% yield was realized.

In summary, the optimal conditions for this cross-coupling consisted of the combination of Cu_2O (10 mol %), **L5** (4 mol %), Cs_2CO_3 (2 equiv.) in acetonitrile or DMSO at 82 ^{O}C or 120 ^{O}C, respectively for 20h under nitrogen atmosphere by following the general coupling procedure.[19]

With the best conditions in hand, we subsequently tested the scope of pyrazole with various aryl halides carrying different substituents to furnish the corresponding products in moderate to excellent yields under the standard reaction conditions, as detailed in Table 2. First, we observed that iodobenzene as substrate with no substituent reacted with 1*H*-pyrazole and gave 83% yield (Table 2, entry, 1). We also noted that both electron-donating and electron-withdrawing substituents, such as nitro, acetyl, methyl, and methoxy were tolerated smoothly on the aryl iodide component in C-N coupling reactions under our reaction conditions. Electron-poor para disubstituted aryl iodides including, 4-iodonitrobenzene and 4-iodoacetophenone coupled with pyrazole in very high yields (98-99%, Table 2, entries 2 and 11), while aryl iodides with electron rich substituent groups including, 4-iodotoluene and 4-iodomethoxy also provided desired products in 45% and 32% yields in MeCN at 82 ^{o}C, respectively (Table 2, entries 12 and 16). However, when the reaction was run in DMSO as solvent at 120 ^{o}C, similar to other literature couplings using *N*-pyridine oxides as ligands,[F14a] electron rich aryl iodides resulted in much higher yields (Table 2, entries 13 and 17). Furthermore, the sterically hindered aryl halides have a very small impact (3-6% reduction yields) on the outcome of the reaction which was evidenced in using ortho substituted aryl iodides, bromides and chlorides compared to their para substituted counterparts (Table 2, entries 6-9 and 19-20). Generally, aryl bromides have lower reactivities than aryl iodides in Ullmann-type couplings, which was the case under our reaction conditions as well, providing C-N bond formation in 50-95% yield, depending on the electronic nature of the aryl halide (Table 2, entries 3, 7, 18 and 19).

Usually, aryl chlorides have not appeared as coupling partners in C-N bond formations in the recent literature; either they do not work or they were not tested, since they are well known for their low reactivity in coupling reactions. However, when a few aryl chlorides with strong electron withdrawing groups were examined using our ligand, they provided coupled products in moderate to good yields (60-78%, Tale 2, entries 4, 5, 8, and 9). To our surprise, even sterically hindered ortho-chloro substrates were able to couple under these reaction conditions.

Table 2. Survey of different substrates and halides with pyrazole.

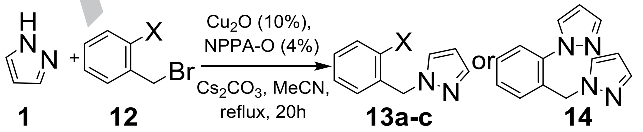


Entry	R	X	Product	Yield (%)[a]
1	H	I	**4**	90
2	4-NO$_2$	I	**3**	98
3	4-NO$_2$	Br	**3**	95
4	4-NO$_2$	Cl	**3**	65
5	4-NO$_2$	Cl	**3**	78[b]
6	2-NO$_2$	I	**5**	89
7	2-NO$_2$	Br	**5**	86
8	2-NO$_2$	Cl	**5**	60
9	2-NO$_2$	Cl	**5**	73[b]
10	3-NO$_2$	I	**6**	88
11	4-COMe	I	**7**	99
12	4-Me	I	**8**	45
13	4-Me	I	**8**	70[b]
14	4-Me	Br	**8**	NR
15	4-Me	Br	**8**	41[b]
16	4-OMe	I	**9**	32
17	4-OMe	I	**9**	51[b]
18	4-CN	Br	**10**	82
19	2-CN	Br	**11**	51
20	2-CN	Br	**11**	70[b]

[a] Isolated yield. [b] The reaction was carried out at 120 °C in DMSO

We have also studied the effect of varying the stoichiometry of pyrzole substrates with various ortho-halide benzyl bromides. When benzyl bromide reacted with pyrazole, the reaction afforded the coupled product **13a** in 87% yield (Table 3, entry 1), while 2-chloro benzyl bromide as a substrate provided the coupled product **13c** in 92%, coupling only at the benzyl bromide side (Table 3, entry 3). However, when 2-iodo benzyl bromide was used, either mono (**13b**) or di-coupled (**14**) was obtained by simply varying the stoichiometry of pyrazole (1.1 or 2.5 equiv., respectively) used in the reaction (Table 3, entry 2). Both products were isolated in very high yields (92-95%). This method is superior to the only example in the literature, showing diamination of ortho halide of benzyl bromide with pyrazole providing product **14** in 73% yield over two steps.[20]

Table 3. Survey of ortho-halide benzyl bromide with pyrazole.

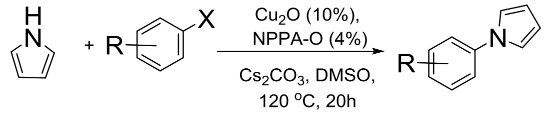


1 **12** **13a-c** **14**

Entry	X	**13**,Yield (%)[a]	**14,** Yield (%)[a]
1	H	87 (13a)	
2	I	92 (13b)	95[b]
3	Cl	92 (13c)	

[a] Isolated yield. [b] 2.5 equiv. of pyrazole was used.

Table 4. Survey of different substrates and halides with pyrrole.

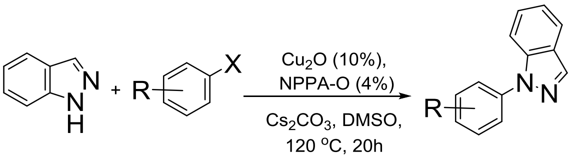


Entry	R	X	Product	Yield (%)[a]
1	H	I	**15**	90
2	4-NO$_2$	I	**16**	97
3	4-NO$_2$	Br	**16**	94
4	4-NO$_2$	Cl	**16**	92
5	2-NO$_2$	I	**17**	80
6	2-NO$_2$	Br	**17**	75
7	2-NO$_2$	Cl	**17**	71
8	4-Me	I	**18**	89
9	4-OMe	I	**19**	75

[a] Isolated yields

Next, the chemistry of Cu$_2$O/ **L5** in C–N cross-coupling with various *N*-heterocyclic compounds such as pyrrole, indazole, and indole with a variety of aryl halides was explored by following the general coupling procedure. In these studies, DMSO was chosen as solvent instead of MeCN for increased solubility of heteroaryls and the ability to increase the reaction temperature up to 120 °C. The results of *N*-arylation of pyrrole are summarized in Table 4. The reaction of pyrrole with electronically neutral or poor aryl halides, including iodide, bromide, and chloride afforded yields higher than 90% (Table 4, entries 1-4). Indeed, sterically hindered ortho-nitro substituted halobenzenes, including chlorides, gave relatively lower yields as compared to the para-isomer, but still in very good yields (7180%, Table 4, entries 5-7). The reaction of aryl iodides with electron-donating substituents groups such as methyl and methoxy substituents proceeded with no reduction in yields (75-89%, Table 4, entries 8 and 9). Overall, coupling of electron rich, poor, or ortho-substituted aryl halides, including chlorides, with pyrrole under our reaction conditions works well to furnish the desired C-N couple products in good to high yields, showing a wide reaction scope.

Table 5. Survey of different substrates and halides with indazole.



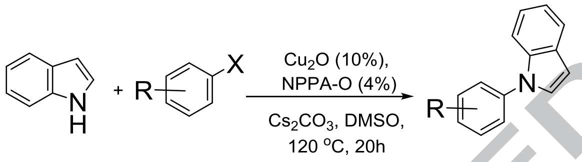
Entry	R	X	Product	Yield (%)[a]
1	H	I	**20**	81
2	4-NO$_2$	I	**21**	86
3	4-NO$_2$	Br	**21**	84
4	4-NO$_2$	Cl	**21**	79
5	2-NO$_2$	I	**22**	80
6	2-NO$_2$	Br	**22**	70
7	2-NO$_2$	Cl	**22**	68
8	4-Me	I	**23**	89
9	4-OMe	I	**24**	70

[a] Isolated yields

Similar to pyrrole couplings, indazole also afforded good to high yields, ranging between 68 and 89% yields, in coupling with various aryl halides, including electron rich, poor, and ortho-substituted iodides, bromides, and chlorides as shown in Table 5. Ortho-substitution results in only 10-12% loss in yields compared to couplings with para-substituted substrates.

Indoles are an important class of heterocycles not only because they are among the most ubiquitous compounds in nature, by being incorporated into the amino acid tryptophan and hormones serotonin and melatonin, but also because they have a wide range of biological activities, including antihypertensive, antiviral, analgesic, antitumor, anti-inflammatory, antimicrobial, and antifungal.[21] Hence, it is not surprising that creating new compounds with indole as the building block is highly important. When indole was used as a nitrogen containing heterocycle in our reaction, indole derivatives were successfully obtained in good to high yields by using a range of aryl halides as shown in Table 6. Following the previous trends of pyrazole, pyrrole, and indazole, indoles also worked well with various aryl halides using Cu_2O/**L5** as catalysts system, since the nature of the aryl halide (electron poor vs rich) appeared to have a negligible effect on the outcome of the results. This makes the indoles useful in general substrate class. These results suggested that, five membered ring *N*-heterocycles such as pyrazole and pyrrole can be efficiently coupled to aryl halides derivatives with higher yields than those of indazole and indole substrates, It can be concluded that, due to steric interactions arising from the peri-like 7-proton of both indazole and indole.[9d]

Table 6. Survey of different substrates and halides with indole.



Entry	R	X	Product	Yield (%)[a]
1	H	I	**25**	95
2	4-NO_2	I	**26**	89
3	4-NO_2	Br	**26**	84
4	4-NO_2	Cl	**26**	81
5	4-Me	I	**27**	80
6	4-OMe	I	**28**	72

[a] Isolated yields

In summary, the use of *N*-phenyl-2-pyridincarboxamide-1-oxide (**L5**) as a ligand with Cu_2O in Ullmann type C-N bond formations between aryl halides and *N*-heteroaryls in common solvents, such as MeCN, DMF, and DMSO at 82-120 °C has been successfully illustrated. The ligand is effective when only 4% equiv is used relative to the substrate. The reaction provided the corresponding products in coupling of electron-rich, electron poor, and ortho-substituted aryl halides, including ortho aryl-chlorides, in good to very good yields. *N*-Arylation is selectively preferred at benzyl position when ortho-halide benzyl bromide is reacted with one equivalent of pyrazole. However, di-*N*-arylation is achieved in very high yields when 2.5 equiv. of pyrazole is used, providing a stoichiometric control over the coupling reaction.

Exploitation of the NPPA, NPPA-N-oxide, and their derivatives in Ullmann type C–O bond formation has been underway, which will be published in the near future.

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Supplementary Data

Supplementary material associated with this article can be found, in the online version, at

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19. General coupling procedure: In 50 mL round bottom flask, aryl halide (1.0 mmol), pyrazole (1.2 mmol), ligand (0.04 mmol), Cu2O (0.10 mmol), cesium carbonate (2.0 mmol), and dry solvent (20 mL) were placed under nitrogen atmosphere. The reaction mixture was heated in oil bath up to specified temperature under constant stirring for 20 h and then allowed to cool to room temperature. The reaction mixture was filtered through a plug of Celite in a fritted filter funnel and washed with ethyl acetate. If DMSO is used as solvent, it is extracted by washing the filtrate with 25 mL water for three times. The organic phase was dried over anhydrous MgSO4 and was removed under reduced pressure to provide the crude product which was purified by column chromatography on silica gel, using hexane and ethyl acetate in 3:1 ratio, respectively, as an eluent.
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Highlights

- N-phenyl-2-pyridincarboxamide-1-oxide as a ligand with Cu_2O in C-N bond formations
- The ligand is effective when only 4% equiv is used relative to the substrate.
- Electron-rich and poor including ortho aryl-chlorides gave good to very good yields.
- Preferred at the benzyl position when ortho-halide benzyl bromide is reacted
- di-N-arylation occurs when ortho-halide benzyl bromide is reacted with excess pyrazole