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N-picolinamides as ligands for Ullmann-type homocoupling reactions

Fehmi Damkaci [a,*], Esra Altay [a], Matthew Waldron [a], Michael A. Knopp [b], David Snow [a], Nicholas Massaro [a]

[a] Department of Chemistry, SUNY Oswego, Oswego, NY 13126, USA
[b] College of Arts and Sciences, University of Maine at Presque Isle, Presque Isle, ME 04769, USA

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ABSTRACT

The use of *N*-phenylpicolinamide (NPPA) as a ligand in Ullmann-type homocoupling reactions of aryl iodides and bromides in common solvents, such as DMF and MeCN has been successfully demonstrated at room temperature. In addition, this work provided the first example of the homocoupling of an aryl chloride at 82 °C, which is a relatively low temperature when compared to regular Ullmann reaction temperatures. Also, NPPA was successfully employed in base—and heat free Suzuki reactions, including electron rich and poor aryl halides with heteroarylboronic acids in moderate yields.

Since its discovery, the Ullmann reaction has become one of the general methods for C–C bond formation in aryl–aryl couplings, C–N bond formation in diamines, and C–O bond formation in diaryl ethers.[1,2] It has been applied to the synthesis of natural products, polyaromatics used as organic conductors or semiconductors possessing unique physical properties, and to the synthesis of efficient and selective chiral biaryl ligands for asymmetric catalysis.[3] The use of the Ullmann coupling has undergone resurgence in the last decade, because new application areas have emerged where the Ullmann coupling showed an advantage over the other methods and the various new modifications have increased its scope.

However, the Ullmann reaction has not been the preferred method, compared to palladium catalyzed methods, because of its main drawback: the necessity of high temperatures.[4] This requirement limits the scope of the Ullmann reaction, since most organic molecules are sensitive to high temperatures.

Several modifications have been developed in order to run the typical Ullmann reaction under milder temperatures, such as ultrasound, sonication, use of different copper sources (e.g. copper(I) salts or copper nanoparticles), use of palladium colloids, and the use of nickel complexes.[1b,1c,2,3] Liebeskind et al. have shown that copper(I)-thiophene carboxylate (CuTC) accomplishes the reductive Ullmann coupling to form C–C bonds at room temperature in a highly polar coordinating solvent, *N*-methylpyrrolidone.[5]

Herein, we demonstrate the use of *N*-phenylpicolinamide (NPPA) as a ligand in Ullmann-type homocoupling reactions of aryl halides in acetonitrile at room temperature. We also present the homo-coupling of the aryl chlorides in the presence of NPPA at 82 °C, which is a much lower temperature requirement than heretofore utilized. To our knowledge, this is the first example of the use of picolinamides as ligands in Ullmann-type coupling reactions. In addition, we also present some selected Suzuki-type aryl–aryl heterocouplings using this methodology.

It has been shown that 2-picolinic acid serves as a ligand in the Ullmann-type C–N bond formation in very low yields.[6] We have decided to prepare certain amides of 2-picolinic acid in order to increase the efficiency of Ullmann-type couplings, because picolinamides potentially provide greater flexibility in tuning the ligand. For our preliminary studies, *N*-phenylpicolinamide (NPPA) was selected as the initial ligand for the Ullmann-type homocoupling reactions in C–C bond formations (Table 1).

2-Iodonitrobenzene was well studied under typical Ullmann reaction conditions and was known for its reactivity only at higher temperatures.[1c] When 2-iodonitrobenzene was reacted with copper in DMF at 120 °C in the absence of NPPA, homocoupled product was obtained in 98% (Table 1, trial 1), which was similar to the literature results. When the reaction was performed at room temperature without NPPA (Table 1, trial 2), starting material was recovered completely, as expected, since Ullmann-type couplings do not generally proceed at room temperature. However, homocoupling in the presence of NPPA provided the product at room temperature in 95% yield (Table 1, trial 3).

Homocoupling reaction in the presence of NPPA in acetonitrile (MeCN) at room temperature gave similar results (98%), the reaction in tetrahydrofuran (THF) provided reasonable yields

* Corresponding author. Tel.: +1 315 312 2698; fax: +1 315 312 5424.
E-mail address: fehmi.damkaci@oswego.edu (F. Damkaci).

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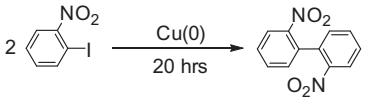
Table 1
The effect of NPPA and solvent on homocoupling[a]



Trial	NPPA	Solvent	Temp	Yield (%)
1	–	DMF	120 °C	98
2	–	DMF	RT	NR
3	+	DMF	RT	95
4	+	MeCN	RT	98
5	+	THF	RT	75
6	+	Dioxane	RT	45

[a] In trials 1 and 2, the reactions were run in the absence of NPPA ligand. NPPA was used in 2 equiv and copper was used in 8 equiv.

(Table 1, trial 5), while the reaction in dioxane at room temperature gave low yields (trial 6). The results with NPPA as a ligand allowed the use of two common solvents (MeCN and DMF) for the Ullmann-type homocouplings at room temperature. MeCN was chosen in the following optimization reactions because of its low boiling point and consequent ease of removal.

It has been known that picolinamide or its N-substituted derivatives coordinate copper ions by acting as N,O-coordinating ligands under neutral conditions, which may also explain the results observed in our coupling reactions by the addition of NPPA.[7] Presumably, copper(I) ion, generated in situ, was coordinated by both the nitrogen of the pyridine and the oxygen of the carbonyl moiety of NPPA[8].

In order to understand the structure–activity relationship of picolinamides in Ullmann type homocouplings, structurally related ligands as shown in Figure 1 have been tested under general coupling conditions[9] (Table 3, Trial 1). The results showed that picolinic acid is better as a ligand compared to picolinamide. However, an *N*-phenyl group on amide nitrogen, as in NPPA, significantly increases the reactivity of the ligand. These results show the importance of the aryl amide moiety, which may have both electronic and steric effects on ligand activity. When 2-pyridinethioamide was used as ligand, starting material was recovered completely showing the importance of the carbonyl oxygen in coordinating to copper.

Several *N*-picolinamide derivatives have been tested in order to further our understanding of the effect of *N*-phenylamide on the activity of the ligand (Table 2). The ligand has been modified on the *N*-phenyl group at the *para*-position with different electron donating and withdrawing groups. However, the survey results demonstrated that the original ligand (NPPA) serves as the best ligand for the homocoupling. When enough time is given for the homocoupling of a highly reactive aryl iodide, almost all ligand derivatives performed well at room temperature. However, when a less reactive aryl bromide was used as substrate, the reaction yields dropped as the *N*-phenyl moiety became more electron rich (Table 2, L2 and L3). When the reaction is limited to 4 h for either aryl iodides or bromides, the reaction yields also dropped with the electron-poor *N*-phenyl group. The results demonstrate that NPPA is the best ligand under these conditions.

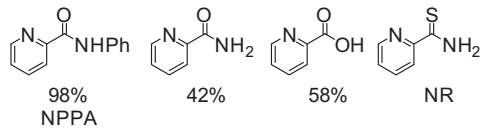
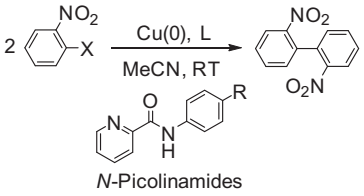


Figure 1. The yields of NPPA derivatives under general conditions to show the structure–activity relationship of the ligand.

Table 2
Screening of *N*-picolinamide derivatives[a]

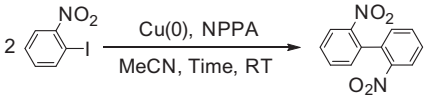


N-Picolinamides

L	R	X = I[a]	X = Br[a]	X = I[b]	X = Br[b]
L1	OMe	85	30		
L2	Me	95	75		
L3	H	98	89	98	46
L4	Cl	95		65	
L5	CN	95	87		24
L6	F	95	30	60	
L7	NO_2	65	NR		

[a] The reactions were run for 20 h.
[b] The reactions were run for 4 h.

Table 3
Time and ligand/starting material ratio effect[a]



Trial	NPPA:SM	Cu	Time (h)	Yield (%)
1	2:1	8	20	>98
2	2:1	8	2	>98
3	1:1	8	8	>98
4	0.5:1	8	4	>98
5	0.5:1	8	2	54
6	1:1	2	20	>98
7	1:1	2	4	>98
8	1:1	1	4	45b

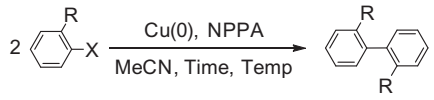
[a] 49% of the starting material is recovered.

It was observed that even 2 h was sufficient time to complete the homocoupling of 2-iodonitrobenzene when the ligand to starting material ratio was 2:1 (Table 3, trial 2). When the reaction was run in less than 2 h, it did not go to completion. In addition, the homocoupling reaction provided a quantitative yield even with 0.5:1 ratio of NPPA to 2-iodonitrobenzene in 4 h (Trial 4). However, when the ratio was decreased to 0.5:1 NPPA:starting material and the time is reduced to 2 h, only 54% of the product was afforded, with the recovery of starting material (Trial 5). More than 2 h is needed to complete the reaction when less than one equivalent of the ligand is used (Trials 6 and 7). The reaction can be accomplished using lower than 0.5 equiv of NPPA at longer reaction times.

It was known that at least 2 equiv of copper was required for coupling of aryl halides in Ullmann-type couplings.[1c] The reaction with NPPA worked well when 2 equivalents of copper was used, and provided the product in a quantitative yield (Table 3, trial 6). When one equivalent of copper was used, almost half of the starting material was recovered, as expected.

Different aryl halides were tested to determine the scope of the reaction using NPPA as the ligand (Table 4). Generally, aryl bromides have low reactivity in Ullmann-type couplings. The best result reported in the literature was obtained by Liebeskind and co-workers with using CuTC ligand.[4] In their study, 2-bromonitrobenzene was homocoupled at 70 °C in NMP as solvent in 86% yield.

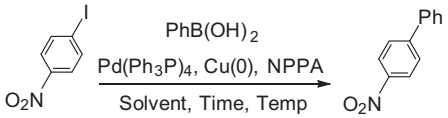
Table 4
Survey of different substrates and halides



Trial	R	X	Temp (°C)	Time (h)	Yield (%)
1	NO_2	Br	RT	20	NR[a]
2	NO_2	Br	RT	20	89
3	NO_2	Br	RT	7	25
4	NO_2	Cl	82	20	>98
5	NO_2	Cl	RT	20	NR
6	C(O)Me	I	RT	20	>98
7	C(O)Me	I	RT	7	96
8	C(O)Me	I	RT	2	62
9	C(O)Me	Br	82	20	NR
10	CO_2Et	I	RT	20	85
11	OMe	I	82	20	NR
12	Me	I	82	20	NR

[a] The reaction was run in the absence of NPPA.

Table 5
Solvent survey for base-free Suzuki type coupling with NPPA



Trial	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	DMF	60	42	59
2	DMF	100	17	62
3	DMF	153	0.5	50
4	MeCN	RT	74	46
5	THF	RT	48	52

[a] 5% $Pd(Ph_3P)_4$ was used.

But to our knowledge, there is no example in the literature showing the homocoupling of 2-bromonitrobenzene at room temperature. In our hands, homocoupling of 2-bromonitrobenzene using NPPA as the ligand afforded the product in 88% yield and gave no product in the absence of ligand at room temperature (Table 4, trial 1 and 2).

Furthermore, we were successful in the homocoupling of 2-chloronitrobenzene, which has not been achieved before, using NPPA as ligand Table 4, trial 4). The reaction does not work at room temperature, but provides high yields (98%) when run in MeCN under reflux. The homocoupling of 2-iodoacetophenone at room temperature was successful even when the reaction was run for 7 h instead of 20 h (Trials 6–8). However, neither 2-bromo- or 2-chloroacetophenone coupled even at higher temperatures (Trial 9). In addition, the homocoupling of 2-iodobenzoic acid ethyl ester using NPPA at room temperature provided the homocoupled product in 85% (Trial 10).

Substrates with *ortho* electron donating groups, did not react even with NPPA; the starting aryl halide was recovered unreacted completely after refluxing for 20 h. This result was not a surprise since it was also the case with CuTC. In addition, substrates with strong electron withdrawing group at the para position did not couple either. Based on the results obtained during these studies, it was demonstrated that Ullmann homocoupling reactions can be accomplished with NPPA addition only with the substrates containing electron-withdrawing at the *ortho* position.

When NPPA is subject to base-free Suzuki type coupling using phenyl boronic acid and 5% Pd(0) catalyst with activated copper bronze, we were successful to obtain coupled product in moderate yields using various solvents (Table 5). The reaction can be run at room temperature as long as 48–74 h or at reflux temperature of DMF for 30 min. to achieve yields around 50–62%. Its base-free and heat-free Suzuki coupling conditions might offer an alternative for complex substrates where base and heat can be destructive.

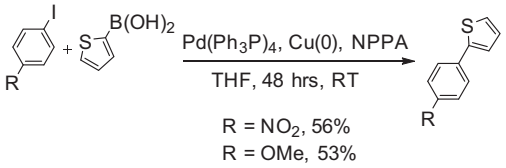


Figure 2. Base-free Suzuki type coupling with NPPA at RT.

The reaction was tested using 2-thiopheneboronic acid (Fig. 2) in order to see the reactivity with hetero aromatic substrates. The reaction did perform similarly at RT with yields ranging 53–56%. The nature of the aryl halide (electron poor vs rich) appeared to have had negligible effect on the outcome of the results which make it useful in general substrate class.

The use of *N*-phenylpicolinamide as a ligand in Ullmann-type homocoupling reactions of aryl iodides and bromides in common solvents, such as DMF and MeCN at room temperature has been successfully demonstrated. In addition, this work provided the first example of the homocoupling of an aryl chloride at 82 °C, which is a relatively low temperature when compared to regular Ullmann reaction temperatures. Also, the ligand was successfully employed in base—and heat free Suzuki reactions, including electron rich and poor aryl halides with heteroarylboronic acids in moderate yields.

It has been demonstrated that the NPPA is effective when 0.5 equiv is used relative to the substrate without any yield loss. Attempts at coupling of electron-rich and electron-neutral aryl halides were unsuccessful. Also, substrates lacking *ortho*-ligating groups did not couple under Ullmann conditions even with the addition of NPPA. These substrates were known not to couple under Ullmann conditions and our methodology has not made any progress in this instance.

Exploitation of the NPPA and its derivatives in Ullmann type C–N bond formation has provided promising results for further investigation, which will be published in the near future..

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.111.

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9. *General homocoupling procedure:* To an oven dried 100 mL round bottom flask with a stir bar, the starting material (1.00 equiv), ligand (2.00 equiv), and activated copper (8.00 equiv) were charged. The flask was vacuumed and purged with nitrogen no less than three times. 15 mL dry acetonitrile was added through a septum via syringe. After stirring the mixture at stated temperature for 20 h (or for the stated duration in the paper), the reaction was immediately vacuum filtered and washed three times with 10 mL of 1M copper acetate solution. The organic layer was washed with 30 mL of H_2O, and dried over $MgSO_4$, filtered, and was kept under vacuo to yield the product.