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Arylation of Azaarylmethylamines with Aryl Chlorides and a $NiBr_2$/NIXANTPHOS-based Catalyst

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Abstract. A nickel-catalyzed coupling of azaarylmethylamines with aryl chlorides has been achieved. NIXANTPHOS together with low cost $NiBr_2$ was successfully developed and optimized to exhibit high reactivity at 2.5 mol % loading. Under optimized reaction conditions, aryl(azaaryl)methylamine products were afforded in good to excellent yields (22 examples, up to 98% yield).

Keywords: NIXANTPHOS; $NiBr_2$; Arylation; Azaarylmethylamines; Aryl Chlorides

Aryl(azaaryl)methylamines are widely found in pharmaceuticals, bioactive substances and as ligands for metal complexes.[1] They have attracted significant attention due to their diverse activity against tumors,[2] viruses,[3] HIV,[4] tuberculosis,[5] iron metabolic disorders,[6] and cortisol dependent diseases.[7] Some prominent examples of aryl(azaaryl)methylamines are illustrated in Figure 1. Classic approaches to the synthesis of aryl(azaaryl)methylamines include addition of organometallic reagents to aldimines,[8] ketimine reduction[9] and C–N coupling reactions.[10] An intramolecular aryl rearrangement to give aryl(azaaryl)methylamines was also reported by Clayden and coworkers.[11] These approaches usually required prefunctionalized starting materials or organolithium reagents, which can limit their scope.

Our group, among others, has strived to develop methods for the catalytic functionalization of weakly acidic sp^3–hybridized C–H bonds via a deprotonative–cross–coupling process (DCCP).[12] These reactions involve reversible *in-situ* deprotonation of the substrates (pronucleophiles) to generate reactive nucleophiles that undergo transmetallation with the catalyst. Considering the value of aryl(azaaryl)methylamines, we recently introduced an efficient palladium-catalyzed approach for the synthesis of aryl(azaaryl)methylamines via *in-situ* deprotonation of (aminomethyl)pyridines followed by arylation with aryl bromides (Scheme 1). This umpolung approach directly provides the arylated tertiary amines without protecting groups or additional activating groups.

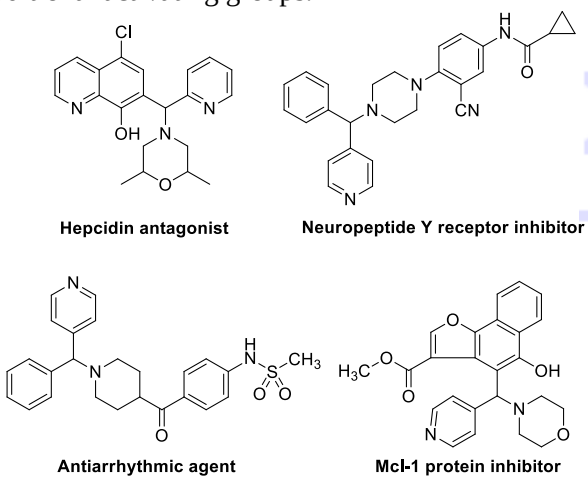
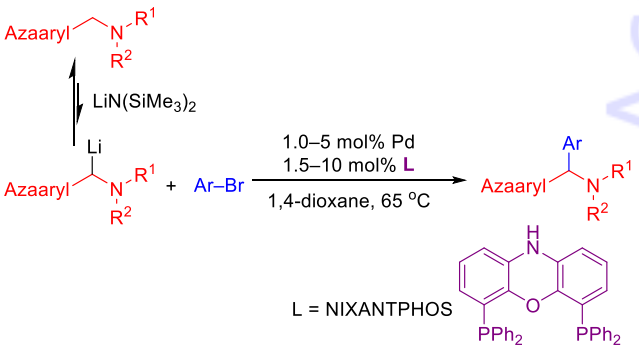
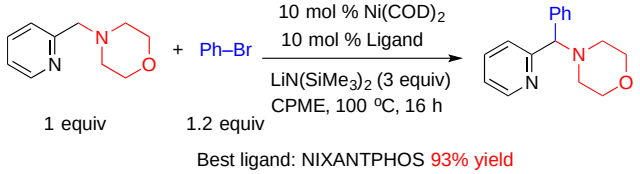


Figure 1. Examples of aryl(azaaryl)methylamines in pharmacologically active compounds.



Scheme 1. Pd-catalyzed arylation of azaarylmethylamines with aryl bromides involving reversible *in-situ* deprotonation of the substrate (aminomethyl)azaarenes.

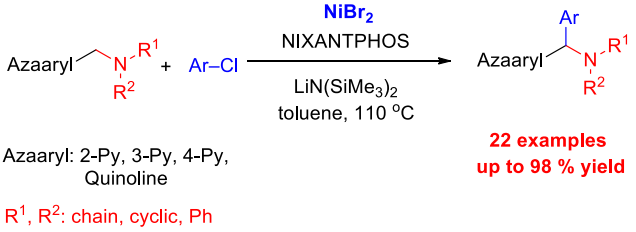
The catalyst for this reaction was based on van Leeuwen's NIXANTPHOS ligand,[13] which we have shown imparts enhanced reactivity to palladium catalysts under basic conditions where the ligand's N–H is deprotonated.[14] We were curious if the enhanced reactivity of (NIXANTPHOS)Pd catalysts would translate to other transition metals. We therefore examined the arylation of 2-pyridylmethyl amine with bromobenzene and $LiN(SiMe_3)_2$ in the presence of 37 of the most common ligands in cross-coupling chemistry.[15] As shown in Scheme 2, the catalyst derived from $Ni(COD)_2$ and NIXANTPHOS proved to be the most active, giving the arylation product in 93% isolated yield.[16] Although only one pyridylmethylamine was examined with the Ni(NIXANTPHOS)-based catalyst, the results appeared promising.



Scheme 2. Preliminary result of arylation of 2-pyridylmethyl morpholine with bromobenzene using $Ni(COD)_2$/NIXANTPHOS catalyst.

An advantage of nickel catalysts over their palladium counterparts is the substantial decrease in cost of Earth-abundant nickel. That said, however, $Ni(COD)_2$ is far from ideal, because it is both expensive and requires special handling precautions due to its air-sensitivity. To improve upon the palladium-based arylation of azaarylmethylamines in Scheme 1, we desired to develop a nickel-based catalyst using a readily available, air-stable, and inexpensive nickel source. Once identified, we planned to expand the scope beyond the singular nickel-catalyzed example in Scheme 1, and to focus on more economical aryl chlorides.

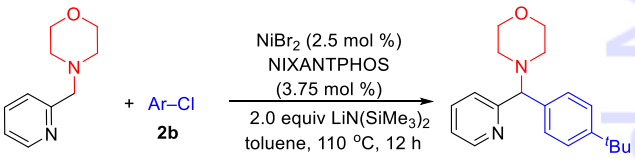
Herein, we report a highly efficient α-arylation of (aminomethyl)pyridines with aryl chlorides using a catalyst formed from $NiBr_2$ and NIXANTPHOS (Scheme 3).



Scheme 3. This work.

Our previous study in Scheme 2 used only bromobenzene as the electrophile. Therefore, using High Throughput Experimentation (HTE) techniques on a 10 umol scale, we initiated studies of the coupling between 4-(pyridin-2-ylmethyl) morpholine **1a** and 4-*tert*-butyl chlorobenzene **2b** with ligand screening on microscale. A total of 44 electronically diverse mono- and bidentate phosphines were examined using $Ni(COD)_2$ as metal source, $LiN(SiMe_3)_2$ as base, and CPME (cyclopentyl methyl ether) as solvent at 110 °C for 12 h (see Supporting Information pg S2 for details). The two most promising ligands from this screen were NIXANTPHOS (**L1**) and JohnPhos (**L2**).[17] We continued with a second lab scale (0.1 mmol) screen examining nickel sources [$NiBr_2$, Cp_2Ni, $Cl_2Ni(PPh_3)_2$ and $Ni(COD)_2$ (5 mol % each)], NIXANTPHOS and JohnPhos, and 3 solvents [CPME, dioxane and toluene] with $LiN(SiMe_3)_2$, 110 °C for 12 h (see Supporting Information pg S5 for details). The top Ni/ligand/solvent combination from this screen was $NiBr_2$/NIXANTPHOS/toluene, affording product **3ab** in 97% assay yield (AY) (Table 1, entry 1). Reducing the catalyst loading to 2.5 and 1 mol % led to 95 and 43% AY (entries 2 and 3). Next, we examined the impact of temperature and found the AY dropped to 75% at 80 °C (entry 4). Reducing the base equivalents from 2 to 1 equiv. led to a significant drop in yield to 22% AY (entry 2). Changing the reaction concentration from 0.1 M to 0.2 M or 0.05 M resulted in a drop in the AY's (76 and 80% yield, entries 5 and 6, respectively).

Table 1. Optimization of α-arylation of azaarylmethylamine **1a** with ArCl **2b**.[a, b]



Entry	$NiBr_2$ /L (mol %)	Conc. (M)	Temp (°C)	Assay yield (%)
1	5/7.5	0.1	110	97
2	2.5/3.75	0.1	110	95(22[c])
3	1/1.5	0.1	110	43
4	2.5/3.75	0.1	80	75
5	2.5/3.75	0.05	110	76
6	2.5/3.75	0.2	110	80

[a] Reactions conducted on a 0.1 mmol scale using 1 equiv of **1a**, 2 equiv of $LiN(SiMe_3)_2$, and 1.2 equiv of ArCl. [b] Yields determined by ^1H NMR spectroscopy of the crude reaction mixtures on a 0.1 mmol scale. [c] 1 equiv. of $LiN(SiMe_3)_2$.

With the optimized conditions in hand (Table 1, entry 2), the scope of 4-(pyridin-2-ylmethyl) morpholine **1a** and different aryl chlorides **2** was explored (Table 2). The product **3aa** was generated from chlorobenzene in 95% yield. Replacing aryl chloride **2a** with its aryl bromide counterpart **2a'** led to a drop in the yield to 79%. It should be noted, however, that these conditions were optimized for aryl chlorides. Alkyl substituted aryl chlorides 4-^{t}Bu (**2b**) and 4-methyl (**2c**) also furnished products in excellent yields (90 and 89%, respectively, for **3ab**

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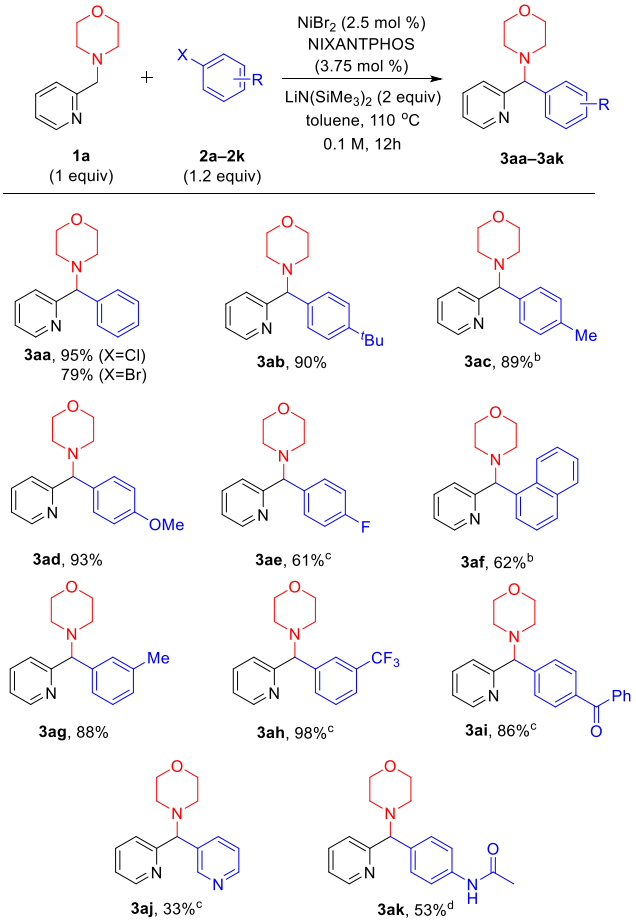
and **3ac**). Electron rich 4-chloroanisole (**2d**) was successfully coupled, delivering **3ad** in 93% yield. 4-Fluorochlorobenzene (**1e**) also underwent coupling in 61% yield to provide **3ae**, although the Ni loading had to be increased to 5 mol %. The sterically hindered 1-naphthyl chloride reacted in 62% yield to provide the expected product (**3af**). Aryl chlorides bearing either 3-methyl or 3-trifluoromethyl groups were suitable cross-coupling partners, furnishing tolyl (**3ag**) and trifluorotolyl (**3ah**) products in 88 and 98% yield, respectively. The substrate 4-chlorobenzophenone could undergo addition of the lithiated pyridyl amine to the carbonyl group. We were pleased to find, however, that the Ni(NIXANTPHOS)-based system exhibited excellent selectivity, providing the diarylmethylamine derivative (**3ai**) in 86% yield. Heteroaromatic 3-chloropyridyl participated in the coupling reaction with **1a** to afford **3aj**, albeit in 33% yield (despite substantial effort to optimize this substrate). Finally, coupling of **1a** with aryl chloride bearing an acetamide group (**2k**) afforded products **3ak** in 53% yield.

Table 2. Substrate scope of aryl chlorides in the arylation of 4-(pyridin-2-ylmethyl)morpholine **1a**.[a]



[a] Reactions conducted on a 0.1 mmol scale using 1 equiv of **1a**, 2 equiv of $LiN(SiMe_3)_2$, and 1.2 equiv of ArCl. Isolated yields after chromatographic purification. [b] 5 mol % Ni. [c] 10 mol % Ni. [d] 4 equiv of $LiN(SiMe_3)_2$

Next, we examined the coupling reactions of various acyclic amines with aryl chloride **2b** (Table 3). When the 2-pyridyl amine was changed from morpholine to N,N-dimethyl- and N,N-diethylamine the corresponding products **3bb** and **3cb** were obtained in 93 and 86% yield, respectively. Under the same conditions, pyrrolidine thiomorpholine and N-methylpiperazine were coupled, generating aryl(2-pyridyl)methylamines in 90, 73, and 82% yield, respectively. In order to achieve a broader scope for our protocol, we examined 4-pyridyl methylamines. N,N-Dimethyl-1-(pyridin-4-yl)methanamine (**1g**) and the morpholine analogue (**1h**) coupled with 4-tert-butyl chlorobenzene to form the desired products **3gb** and **3hb** in 60 and 89% yield, respectively. In addition, 1-methyl-4-(pyridin-4-ylmethyl)piperazine (**1i**) furnished product **3ib** in 97% yield. Despite significant optimization, the 3-pyridylmethyl amine 4-(pyridin-3-ylmethyl)morpholine yield could not be raised above 61%. The isoquinoline derivative N,N-dimethyl-1-(quinolin-2-yl)methanamine (**1k**) furnished the coupling product **3kb** in 80% yield. N-Methyl-N-(pyridin-2-ylmethyl)aniline (**1l**) underwent coupling to provide the product **3lb** in 56% yield with 10 mol % catalyst. We tested the coupling of benzyl amine with **2b**, however, no product could be observed and starting material was recovered. The C-N coupling (Buchwald-Hartwig coupling) was also not observed.

Table 3. Substrate scope of azaarylmethylamines in the arylation of aryl chloride **2b**.[a]

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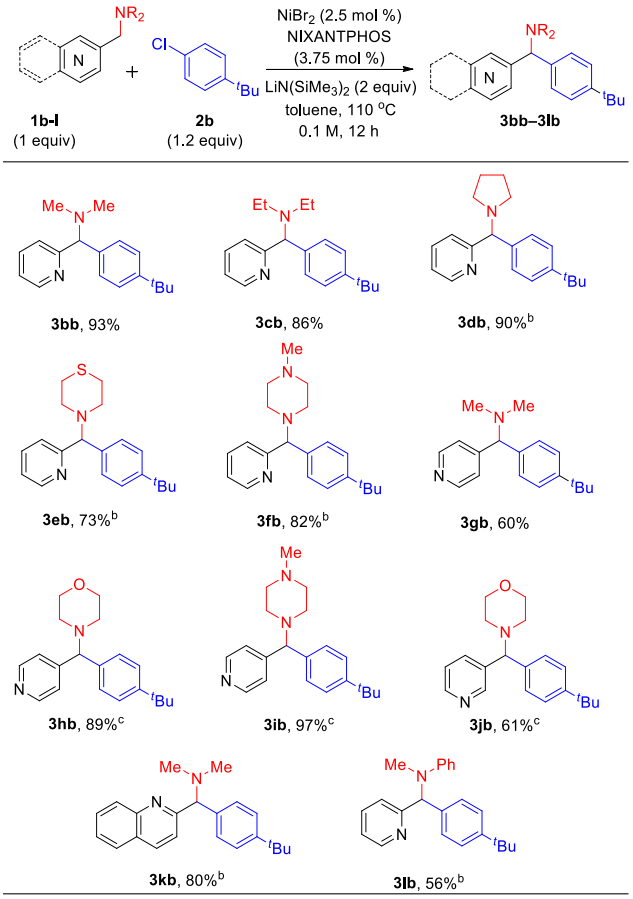
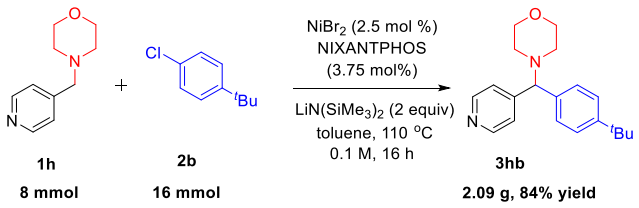


[a] Reactions conducted on a 0.1mmol scale using 1 equiv of **1b-1i**, 2 equiv of $LiN(SiMe_3)_2$, and 1.2 equiv of ArCl. Isolated yields after chromatographic purification. [b] 10 mol % Ni. [c] 5 mol % Ni.

In order to investigate the potential scalability of our protocol (Scheme 4), we conducted the arylation of 4-(pyridin-4-ylmethyl)morpholine **1h** with 4-*tert*-buty chlorobenzene **2b** on gram scale. The desire coupled product **3hb** was isolated in 84% yield (2.09 g).



Scheme 4. Gram scale synthesis of **3hb.**

In conclusion, we report an efficient nickel-catalyzed arylation of azaarylmethylamines with aryl chlorides. Various aminomethyl azaarenes and aryl chlorides are easily coupled to provide attractive intermediates for the synthesis of biologically active compounds. The most significant advance is replacing palladium with an inexpensive and easily handled nickel source, $NiBr_2$. In several cases, the loading of the nickel-based catalyst is lower than the palladium analogue.

Finally, a key finding of this work is that the combination of nickel and NIXANTPHOS outperformed other nickel ligand combinations in the coupling of azaarylmethylamines with aryl chlorides under the conditions examined. These results suggest that the high reactivity of the Pd(NIXANTPHOS) catalyst under conditions where the NIXANTPHOS N–H is deprotonated are translatable to nickel and perhaps other metals. We are currently exploring this hypothesis as well as attempting to develop an enantioselective version of this reaction.

Experimental Section

1. General procedure for the arylation of azaarylmethylamines.

An oven-dried microwave vial equipped with a stir bar was charged with $LiN(SiMe_3)_2$ (66.9 mg, 0.4 mmol, 2.0 equiv) under a nitrogen atmosphere in the glovebox. 4-(Pyridin-2-ylmethyl)morpholine (35.6 mg, 0.2 mmol, 1.0 equiv) and 4-*t*-Bu-chlorobenzene (40.5 mg, 0.24 mmol, 1.2 equiv) were added by syringe in the glovebox. Next, 1 mL stock solution containing $NiBr_2$ (1.1 mg, 0.005 mmol) and NIXANTPHOS (4.2 mg, 0.0075 mmol) in toluene was added under a nitrogen atmosphere via syringe in the glovebox. The microwave vial was sealed with a cap and the reaction was stirred at 110 °C for the specified time then allowed to cool to room temperature. The reaction mixture was quenched with H_2O (0.2 mL) and passed through a short pad of silica gel and eluted with ethyl acetate (1 mL * 3). The combined organics were concentrated in vacuo. The crude residue was purified by flash column chromatography to yield the monoarylated azaarylmethylamine derivatives 3.

2. Procedure for the gram scale synthesis.

An oven-dried 100 mL Schlenk tube equipped with a stir bar was charged with 4-(pyridin-4-ylmethyl)morpholine 1h (1.44 g, 8.0 mmol). The Schlenk tube was sealed with a rubber septum and was connected to a Schlenk line, evacuated, and refilled with nitrogen (repeated three times). A solution (prepared in the glove box) of aryl chloride 2b (2.70 g, 16.0 mmol) in 5 mL anhydrous toluene was added to the Schlenk tube via syringe through the rubber septum. A solution (prepared in the glove box) containing $NiBr_2$ (44 mg, 0.2 mmol) and NIXANTPHOS (168 mg, 0.3 mmol) in 5 mL anhydrous toluene was added to the Schlenk tube via syringe through the rubber septum. Next, a solution of $LiN(SiMe_3)_2$ (2.68 g, 16.0 mmol) in 30 mL anhydrous toluene was added by syringe through the rubber septum. The reaction mixture was stirred for 16 h in total at 110 °C, opened to air, and quenched with 10 mL of H_2O. The layers were separated and the aqueous layer was extracted with DCM (3X10 mL). The combined organic layers were concentrated in *vacuum*. The crude material was loaded onto a deactivated silica gel column via pipette and purified by flash chromatography on silica gel (eluted with

Methanol : DCM = 1:30) to give the product (2.09 g, 84% yield) a white solid. The ^{1}H and $^{13}C\{^{1}H\}$ NMR data for this compound match the literature data.

Acknowledgements

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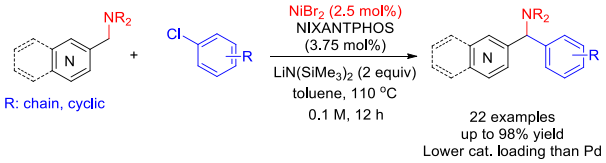
COMMUNICATION

Arylation of Azaarylmethylamines with Aryl Chlorides and a $NiBr_2$/NIXANTPHOS-based Catalyst



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