Organic LETTERS

Letter

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Palladium-Catalyzed Benzylic C−H Arylation of Azaarylmethylamines

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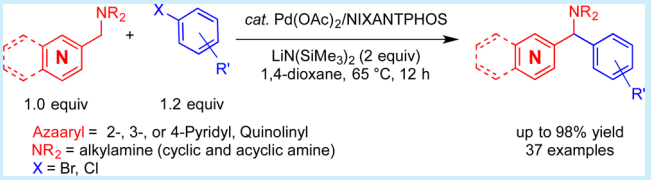
Supporting Information

ABSTRACT: A direct C−H functionalization approach to produce aryl(azaaryl)methylamines from azaarylmethylamines without directing groups is described. Under conditions where the azaarylmethylamines' C−H is reversibly deprotonated, a $Pd(OAc)_2$/NIXANTPHOS-based catalyst couples the resulting carbanions with various aryl halides to provide aryl(azaaryl)methylamines. This umpolung strategy directly provides tertiary amines without protecting or activating groups.



Pyridine and quinoline derivatives are important heterocycles that are present in a broad range of biologically active natural products and pharmaceutically relevant compounds.[1] Aryl(azaaryl)methylamines are prominent in biologically active small molecules, exhibiting antitumor,[2] antivirus,[3] anti-HIV,[4] and antihistamine activities[5] (Figure 1). Furthermore, recent statistical studies indicate that the prominence of heteroaromatic rings in marketed oral drugs is increasing.[6]

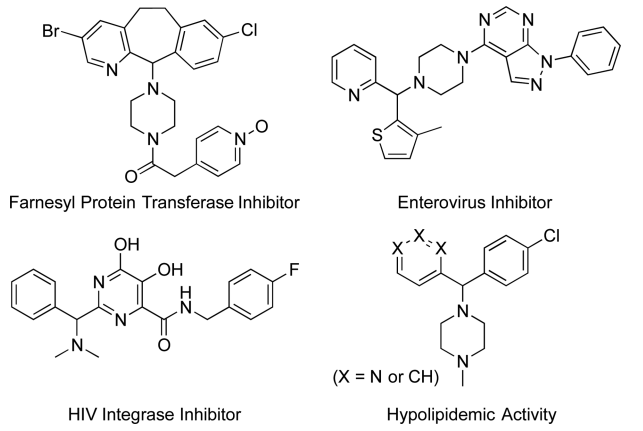


Figure 1. Selected pharmacologically active compounds containing aryl(azaaryl)methylamines.

Conventional approaches to the synthesis of 1,1-diarylmethylamine derivatives[7] include substitution reactions with amine nucleophiles, addition of aryl or azaaryl organometallic reagents to imines, and reduction of imines.[8] Despite the popularity of these methods, they involve prefunctionalized electrophiles or nucleophiles. Transition-metal-catalyzed cross-coupling reactions also represent an attractive approach.[7d] The direct C−H functionalization of amino alkyl moieties ($R'CH_2NR_2$), however, is challenging.[9] Therefore, activated substrates, such as Boc-protected amines, ketimines, and (η^6-benzylamine)$Cr(CO)_3$ complexes, have been employed to facilitate deprotonation of C−H bonds adjacent to nitrogen (Figure 2).[10] The activating groups necessary in Figure 2 to increase reactivity are often subsequently transformed into the desired functional groups or excised from the product entirely, decreasing the synthetic efficiency.

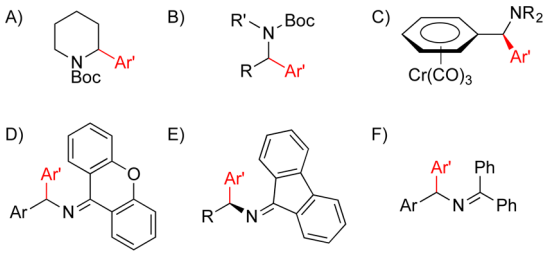


Figure 2. Representative synthetic intermediates with directing groups (A, B) and activating groups (C−F) employed in metal-catalyzed C−H functionalization adjacent to nitrogen.

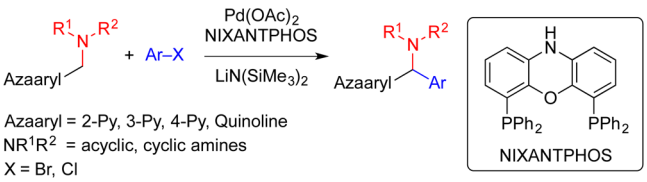
Considering the importance of aryl(azaaryl)methylamines, the development of in situ deprotonation/arylation strategies for their synthesis that do not employ activating groups would be valuable. Based on our experience in deprotonative cross-coupling reactions[10c−f,11] with weakly acidic substrates, we hypothesized that the reversible deprotonation of (aminomethyl)pyridines in the presence of a palladium catalyst should be possible.

Received: October 6, 2015

DOI: 10.1021/acs.orglett.5b02898
Org. Lett. XXXX, XXX, XXX−XXX

Herein, we report a practical method to prepare aryl(azaaryl)methylamines from (aminomethyl)pyridines and aryl halides using a Pd–NIXANTPHOS-based catalyst (Scheme 1).

Scheme 1. Palladium-Catalyzed Benzylic C–H Arylation with Azaarylmethylamines



This approach affords single-step access to aryl(azaaryl)methylamines from simple starting materials. Notably, to the best of our knowledge, the direct functionalization of aminomethyl azaarenes has not been successfully achieved prior to this work.

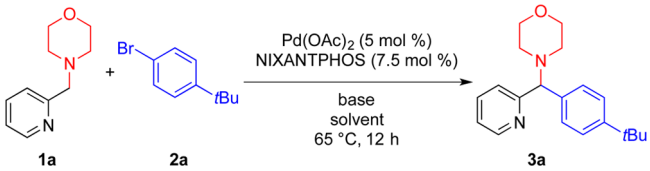
We anticipated two challenges to advancing a successful deprotonative cross-coupling process (DCCP) with (aminomethyl)pyridine derivatives: (1) introduction of conditions for the in situ deprotonation of the weakly acidic C–H's of the substrate and (2) identification of a catalyst capable of promoting coupling of the resulting organolithium, -sodium, or -potassium derivatives with aryl halides. In the latter case, we have found that palladium complexes of van Leeuwen's NIXANTPHOS ligand[12] outperform other Pd–phosphine complexes in this class of reactions. As such, it has become our "go to" ligand for new substrate classes. Concerning the deprotonation step, the pK_a of the sp^3-hybridized C–H's of 2-(aminomethyl)pyridines are unknown, although that of 2-methylpyridine has been determined to be 34 in THF.[13] The high pK_a value of these substrates suggests that alkoxide and silylamide bases are good starting points. Additionally, palladium-catalyzed benzylic arylations of pyridine derivatives have become a powerful method to construct aryl(azaaryl)methane derivatives.[14]

We initially tested the reactions of 2-(morphorinomethyl)pyridine (**1a**) with 1-bromo-4-*tert*-butylbenzene using Pd(OAc)$_2$ (5 mol %) and NIXANTPHOS (7.5 mol %) in THF at 65 °C. Six bases [LiO-*t*-Bu, NaO-*t*-Bu, KO-*t*-Bu, LiN(SiMe$_3$)$_2$, NaN(SiMe$_3$)$_2$, and KN(SiMe$_3$)$_2$] were employed, and the results are displayed in entries 1–6 of Table 1.

Although MO-*t*-Bu bases [M = Li, Na, K] did not generate the desired product **3a** (entries 1–3), MN(SiMe$_3$)$_2$ bases (M = Li, Na, K) were all very promising, affording 80–87% assay yield (AY) of the cross-coupling product **3a** (entries 4–6). The most promising result was obtained with LiN(SiMe$_3$)$_2$ (87% AY as determined by ^{1}H NMR, entry 4). We next screened other ethereal solvents (DME, CPME, 1,4-dioxane) (entries 7–9). Of these, 1,4-dioxane led to 90% AY of the desired product (entry 9). Examination of the stoichiometry indicated use of a 1:1.2:2 ratio of pyridylmethylamine (**1a**)/1-bromo-4-*tert*-butylbenzene (**2a**)/LiN(SiMe$_3$)$_2$ rendered 98% AY of **3a**, leading to 92% isolated yield (entry 11). Use of a stoichiometric amount of 1-bromo-4-*tert*-butylbenzene (**2a**) or lower catalyst loading [2.5 mol % Pd(OAc)$_2$ and 3.75 mol % of NIXANTPHOS] resulted in incomplete conversion at 65 °C after 12 h (entries 12–13). The optimized conditions (entry 11, Table 1) were then used to define the substrate scope.

The scope of the arylation was initially explored with 2-(cyclic amino)methylpyridines (**1**) using aryl bromides

Table 1. Selected Optimization of Pd-Catalyzed C(sp^3)–H Arylation of 1a with 2a



1a 2a 3a

entry	base	1a/2a/base	solvent[a]	yield[b] (%)
1	LiO-*t*-Bu	1:1.5:3	THF	0
2	NaO-*t*-Bu	1:1.5:3	THF	0
3	KO-*t*-Bu	1:1.5:3	THF	0
4	LiN(SiMe$_3$)$_2$	1:1.5:3	THF	87
5	NaN(SiMe$_3$)$_2$	1:1.5:3	THF	80
6	KN(SiMe$_3$)$_2$	1:1.5:3	THF	83
7	LiN(SiMe$_3$)$_2$	1:1.5:3	DME	82
8	LiN(SiMe$_3$)$_2$	1:1.5:3	CPME	85
9	LiN(SiMe$_3$)$_2$	1:1.5:3	1,4-dioxane	90
10	LiN(SiMe$_3$)$_2$	1:1.5:2	1,4-dioxane	92
11	LiN(SiMe$_3$)$_2$	1:1.2:2	1,4-dioxane	98 (92)[c]
12	LiN(SiMe$_3$)$_2$	1:1:1.5	1,4-dioxane	73[d]
13	LiN(SiMe$_3$)$_2$	1:1.2:2	1,4-dioxane	64[e]

[a]Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), cyclopentyl methyl ether (CPME), and 1,4-dioxane (dioxane). [b]Yields were determined by ^{1}H NMR analysis of unpurified reaction mixtures with internal standard CH_2Br_2. [c]Isolated yield. [d]14% of **1a** remained. [e]2.5 mol % of Pd(OAc)$_2$ and 3.75 mol % of NIXANTPHOS.

(Scheme 2). Morpholine, pyrrolidine, and *N*-methylpiperazine were coupled with aryl bromides bearing various substituents, generating aryl(2-pyridyl)methylamines in good to excellent isolated yields (65–98%). The arylated products **3b–d** were obtained in 78–83% yield with bromobenzene and 1-bromonaphthalene. Under the same reaction conditions, chlorobenzene was also a suitable coupling partner, providing **3b** in 78% yield. Aryl bromides bearing electron-donating 4-NMe$_2$ and 4-OMe resulted in coupling products **3e–h** in 71–94% yield. Aryl bromides with electron-withdrawing 4-F and 3-CF$_3$ groups were well tolerated and provided aryl(2-pyridyl)methylamines **3i–k** in 71–94% yield. Heterocyclic 3-bromopyridine was also a suitable coupling partner to generate dipyridylmethyl morpholine **3l** in 65% yield. The reactions with 1 mol % of catalyst generally occurred in good yields (71–75% yield, **3d**, **3g**, and **3i**). To illustrate the scalability of our method, we conducted coupling of 2-(morphorinomethyl)pyridine (**1a**, 10 mmol) with 1-bromo-4-fluorobenzene using 4 mol % of catalyst. The coupling product **3m** was isolated in 96% yield (2.61 g).

Next, we turned our attention to acyclic amines. The optimized arylation conditions employed with cyclic amines were easily transferable to *N*,*N*-dimethyl- or -diethylamine derivatives with a variety of aryl bromides. Thus, aryl bromides with neutral (4-*t*-Bu, 3-Me), electron-donating (4-OMe, 4-NMe$_2$), or electron-withdrawing (4-F, 4-Cl, 3-OMe, 3-CF$_3$) substituents coupled with 2-(*N*,*N*-dialkylaminomethyl)pyridine, providing the cross-coupling products **4a–o** in 60–98% yield (Scheme 3). The yields with *N*,*N*-dimethylamine derivatives are slightly higher than those with cyclic amines. Several relatively challenging substrates (1-bromo-4-trifluoromethylbenzene and 5-bromobenzofuran) were also competent coupling partners, albeit in reduced yields (**4i,j**, 60–66% yield). While 1-bromonaphthylene furnished coupling product **4k** in 69%

DOI: 10.1021/acs.orglett.5b02898
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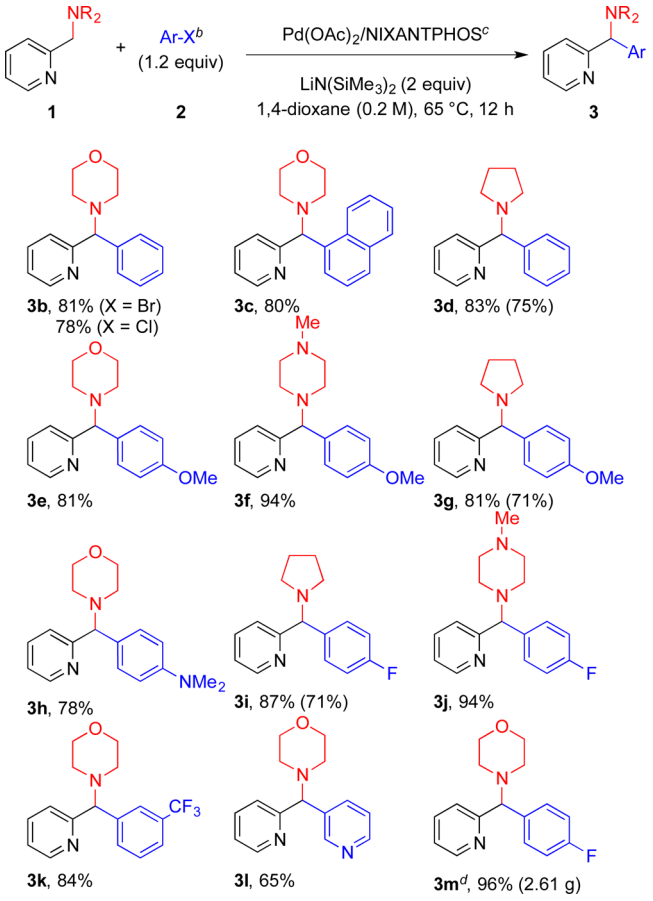
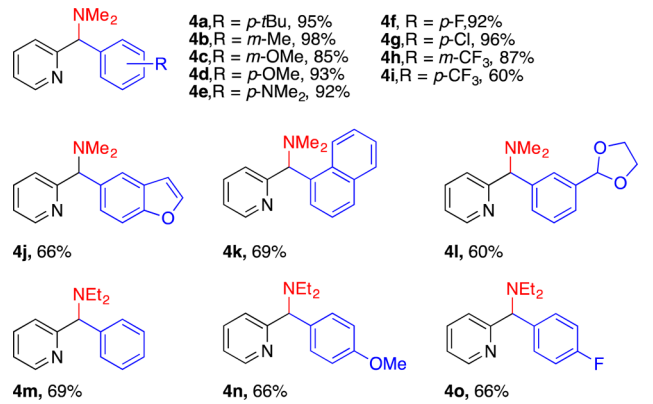
Scheme 2. Pd-Catalyzed C(sp^3)−H Arylation of 2-Pyridylmethylamines 1 with Aryl Bromides 2[a]



[a]Isolated yields. [b]X = Br was used unless noted. [c]5 mol % of $Pd(OAc)_2$ and 7.5 mol % of NIXANTPHOS and the yields in parentheses with 1 mol % of $Pd(OAc)_2$ and 1.5 mol % of NIXANTPHOS. [d]4 mol % of $Pd(OAc)_2$ and 6 mol % of NIXANTPHOS.

Scheme 3. Benzylic Cross-Coupling of 2-(Dialkylaminomethyl)pyridine 1 with Aryl Bromides 2[a]

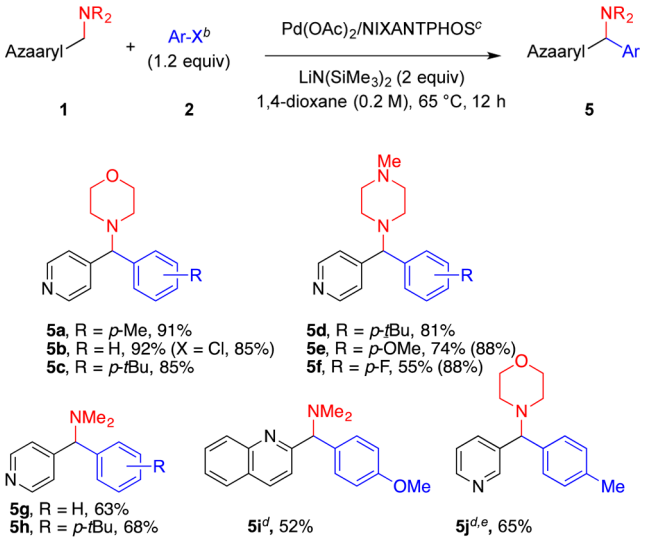


[a]Isolated yields.

yield, the sterically more hindered 2-bromotoluene failed to provide the desired product (<2% yield). 2-(3-Bromophenyl)-1,3-dioxolane generated acetal-protected aldehyde product **4l** in 60% yield. When the same conditions were applied to 2-(*N*,*N*-diethylaminomethyl)pyridine, the desired products **4m**−**o** were isolated in 66−69% yield. Sterically more hindered 2-(*N*-benzyl-*N*-methylaminomethyl)pyridine did not react (<2% yield). Similar results were observed in related reactions by Baudoin and our groups with bulkier substituents on nitrogen.[11o,15]

The above results led us to wonder if this method would be limited to 2-pyridyl derivatives because it requires a directed metalation for the deprotonation. To answer this question, other heterocyclic substrates were tested. Although the pK_a's of 4-pyridylmethylamines are not reported, 4-methylpyridine has a pK_a of 32.2 in THF.[13] As shown in Scheme 4, 4-pyridylmethyl-

Scheme 4. Benzylic Cross-Coupling of Azaarene Derivatives



[a]Isolated yields. [b]X = Br unless noted. [c]1 mol % of $Pd(OAc)_2$ and 1.5 mol % of NIXANTPHOS and the yields in parentheses with 5 mol % of $Pd(OAc)_2$ and 7.5 mol % of NIXANTPHOS. [d]5 mol % of $Pd(OAc)_2$ and 10 mol % of NIXANTPHOS. [e]The reaction was conducted in THF at 110 °C with $KN(SiMe_3)_2$ instead of $LiN(SiMe_3)_2$.

amine derivatives were excellent substrates, providing coupling products in 55−92% yield (**5a**−**h**) with 1 mol % catalyst loading. These results indicate that chelation of the base to the 2-pyridyl group is not necessary for the reversible deprotonation step of this DCCP.

Additional heterocycles were also amenable to the DCCP. Under the conditions used for 2-pyridylamines, a 2-(aminomethyl)quinoline derivative underwent a direct arylation reaction in 52% yield (**5i**). The least acidic substrate tested in this study was the 3-pyridylmethylamine derivative. The pK_a of 3-methylpyridine is 37.7 in THF.[13] After extensive optimization of bases, solvents, and temperature, we were able to achieve coupling in the presence of 2 equiv of $KN(SiMe_3)_2$ in THF at 110 °C, resulting in arylation product **5j** in 65% yield.

In summary, we report the first direct palladium-catalyzed *benzylic C(sp^3)−H* arylation of cyclic and acyclic aminomethyl-substituted azaarenes with aryl bromides. A variety of aryl(azaaryl)methylamines were prepared in good to excellent yields from readily accessible tertiary aminomethyl azaarenes. It is noteworthy that addition and removal of directing groups was not necessary with these substrates, facilitating their streamlined synthesis. This new method enables the rapid preparation of druglike molecules using straightforward

DOI: 10.1021/acs.orglett.5b02898
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techniques that are ideal for applications in medicinal chemistry.[16]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02898.

Spectroscopic characterization data and procedures for preparation of all new compounds (PDF)

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Author Contributions

‖B.-S.K. and J.J. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by NIH/NIGMS (GM 104349). J.J. thanks CONACyT (México) for fellowships. F.G. thanks the China Scholarship Counsel for fellowships.

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(16) From preliminary experiments screening 37 different Ni(phosphine)-based catalysts in the coupling of **1a** with bromobenzene, it was found that the Ni(NIXANTPHOS)-based catalyst gave the highest product/internal standard ratio; see: Cao, X.; Sha, S.-C.; Li, M.; Kim, B.-S.; Morgan, C.; Huang, R.; Yang, X.; Walsh, P. J. *Chem. Sci.* **2016**, DOI: 10.1039/C5SC03704B.

DOI: 10.1021/acs.orglett.5b02898
Org. Lett. XXXX, XXX, XXX−XXX